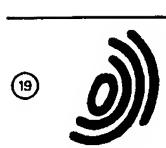


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⑪ Publication number:

0 289 227 B1

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EUROPEAN PATENT SPECIFICATION

⑯ Date of publication of patent specification: 08.04.92 ⑮ Int. Cl. 5: C07D 233/64, C07D 403/06,
A61K 31/415, A61K 31/435
⑯ Application number: 88303646.9
⑯ Date of filing: 22.04.88

⑯ Substituted Imidazolyl-alkyl-piperazine and -diazepine derivatives.

⑯ Priority: 24.04.87 US 42181
⑯ Date of publication of application:
02.11.88 Bulletin 88/44
⑯ Publication of the grant of the patent:
08.04.92 Bulletin 92/15
⑯ Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE
⑯ References cited:
BE-A- 820 242
US-A- 3 362 956
US-A- 3 491 098

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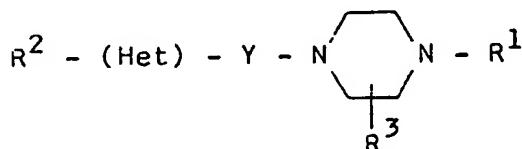
Description

This invention relates to substituted imidazolyl-alkyl-piperazine and diazepine derivatives, the pharmaceutically acceptable salts thereof, methods of making these compounds, and pharmaceutical compositions containing these compounds. The compounds of this invention are calcium entry blockers having selectivity for cerebral blood vessels, and have protective activity against some of the deleterious effects resultant upon cerebral ischemia. The compounds of this invention are, therefore, useful for treating mammals having a variety of disease states, such as stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, and also for treatment of spinal injuries.

Substituted piperazines have been described as having a variety of pharmaceutical activities.

For example, U.S. Patent No. 3,362,956 and its CIP 3,491,098, disclose a series of substituted piperazines to be useful as tranquilizers, sedatives, adrenolytic agents, hypothermic agents, anti-convulsants, hypotensive agents and cardiovascular agents. For example, in the '956 patent, compounds of the formula

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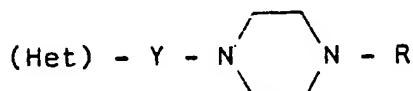


25

wherein R^1 is a lower-alkyl, hydroxy-lower alkyl, phenyl or substituted-phenyl, phenyl-lower-alkyl, or substituted-phenyl-lower-alkyl, benzhydryl or substituted benzhydryl, phenyl-lower-alkenyl or substituted phenyl-lower-alkenyl, or pyridyl radical; R^2 is hydrogen or from one to two lower-alkyl radicals; Y is lower-alkylene of from one to six carbon atoms; and Het is a heterocyclic radical selected from the group consisting of bicyclic aromatic nitrogen heterocyclic radicals having fused five and six membered rings and containing from two to three ring nitrogen atoms which can be in any position of the two rings, for example, radicals derived from indazole (e.g. 2-azaindole, 4-azaindole, 5-azaindole, 6-azaindole, 7-azaindole), pyrrolo-[2,3-d]-pyrimidine, benzimidazole and pyrido[2,1-c]-s-triazole; a benz[g]-3-indolyl radical; a 4(5)-imidazolyl radical; a 3-thianaphthetyl radical; a 3-quinolyl radical; a 3,4-dihydro-1-isoquinolyl radical; or 1,2,3,4-tetrahydro-1-isoquinolyl radical or such heterocyclic radicals substituted in any available position by from one to three substituents, defined hereinafter as R^2 , for example, methyl, ethyl, propyl, and isobutyl; lower-alkoxy, for example, methoxy, ethoxy, propoxy, and butoxy; halogen, including fluorine, chlorine, bromine, and iodine; lower-alkylmercapto, for example, methylmercapto, ethylmercapto, propylmercapto, and isobutylmercapto; lower-alkylsulfinyl, for example, methylsulfinyl, ethylsulfinyl, propylsulfinyl, and isobutylsulfinyl; lower-alkylsulfonyl, for example, methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl; trifluoromethyl; hydroxy; methylenedioxy; or ethylenedioxy, wherein the lower-alkyl moiety of the said substituents contain from one to four carbon atoms; are disclosed.

In the '098 patent compounds of the formula

45



50

wherein R is hydrogen or a lower-alkyl, hydroxy-lower-alkyl, phenyl, phenyl-lower-alkyl, benzhydryl, phenyl-lower-alkenyl, cycloalkyl-lower-alkyl, or pyridyl radical; Y is lower-alkylene of from one to six carbon atoms; and Het is a 4(5)-imidazolyl radical; are disclosed.

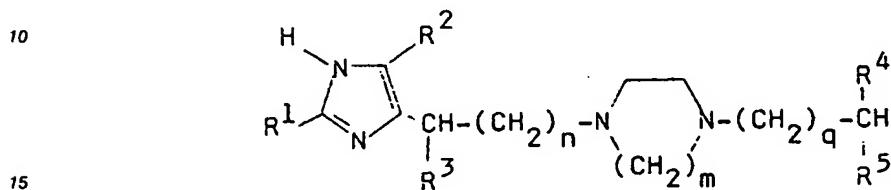
None of the prior art teaches 4(5)-imidazolyl-substituted piperazine or diazepine derivatives substituted in the manner of this invention which are useful for treating mammals having a variety of disease states, such as stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as

Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, and also for treatment of spinal injuries.

SUMMARY OF THE INVENTION

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A first aspect of this invention encompasses compounds having the structures represented by Formula A:



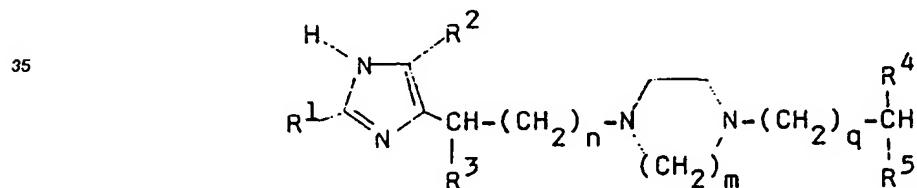
FORMULA A

20 wherein:

- R¹ is aryl;
- R² is aryl, lower alkyl, or hydrogen;
- R³ is lower alkyl, hydroxy, or hydrogen;
- R⁴ is aryl;
- R⁵ is aryl;
- m is two or three;
- n is zero, one or two,
- provided that when R³ is hydroxy, n is one or two; and
- q is zero, one, two, or three;

30 and the pharmaceutically acceptable salts thereof.

A further aspect of the present invention encompasses methods of making compounds of Formula A



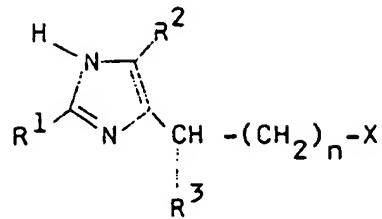
FORMULA A

wherein:

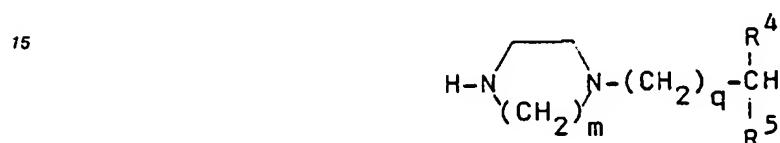
- R¹ is aryl;
- R² is aryl, lower alkyl, or hydrogen;
- R³ is lower alkyl, hydroxy, or hydrogen;
- R⁴ is aryl;
- R⁵ is aryl;
- m is two or three;
- n is zero, one or two,
- provided that when R³ is hydroxy, n is one or two; and
- q is zero, one, two, or three;

and the pharmaceutically acceptable salts thereof, which comprises

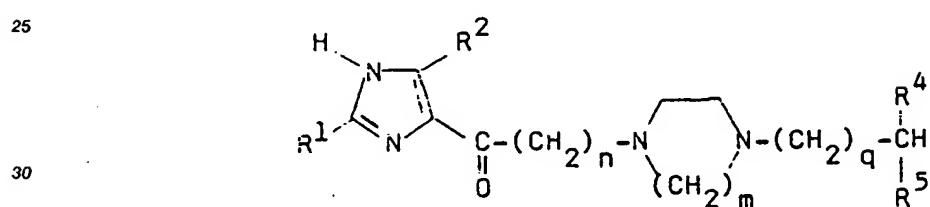
55 (a) condensing a compound of the formula



10 wherein n, R¹ and R² are as defined above, R³ is hydrogen or lower alkyl, and X is a halogen atom, with a compound of the formula



20 wherein m, q, R⁴ and R⁵ are as defined above; or
b) reducing a compound of the formula



35 wherein R¹, R², R⁴, R⁵, m, and q are as defined above and n is one or two, to form a compound of formula A wherein R³ is hydroxy; or
c) converting a free base compound of formula A to its acid addition salt; or
d) converting an acid addition salt of a compound of formula A to a free base compound of formula A; or
e) converting an acid addition salt of a compound of formula A to another acid solution salt of a compound of formula A.

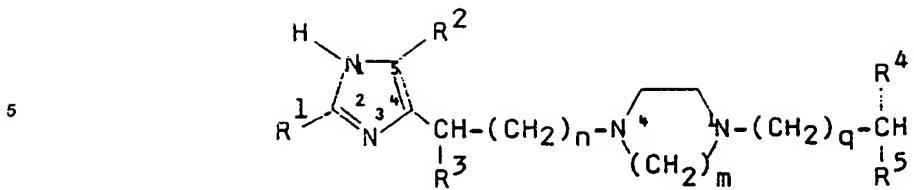
40 A still further aspect of the present invention encompasses methods of treating a mammals having a variety of disease states, such as stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, and also for treatment of spinal injuries, comprising administering a therapeutically effective amount of compound of Formula A to a mammal.

45 Another aspect of the present invention encompasses pharmaceutical formulations comprising a compound of Formula A and a pharmaceutically acceptable excipient.

DETAILED DESCRIPTION OF THE INVENTION

50 Definitions

The numbering of the piperazines and diazepines of the present invention is as follows:



10 The compounds of the invention will be named using the above-shown numbering system as 1-[di-aryl]-alkyl-4-[2-and/or 5-substituted- imidazoly]-optionally-substituted-alkyl]-piperazines and -diazepines. Some representative compounds are named as follows:

the compound of Formula A where R¹ is 4-methylphenyl, R² is methyl, R³ is hydrogen, R⁴ is phenyl, R⁵ is phenyl, m is 2, n is 0 and q is 0, is named "1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine";

the compound of Formula A where R¹ is 4-methylphenyl, R² is hydrogen, R³ is hydrogen, R⁴ is phenyl, R⁵ is phenyl, m is 2, n is 0, and q is 0, is named "1-diphenylmethyl-4-[(2-(4-methylphenyl)-1H-imidazol-4-yl)methyl]piperazine";

the compound of Formula A where R¹ is phenyl, R² is methyl, R³ is methyl, R⁴ is phenyl, R⁵ is phenyl, m is 2, n is 0 and q is 0, is named "1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine";

the compound of Formula A where R¹ is phenyl, R² is methyl, R³ is hydroxy, R⁴ is phenyl, R⁵ is phenyl, m is 2, n is 1 and q is 0, is named "1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine";

25 the compound of Formula A where R¹ is phenyl, R² is methyl, R³ is hydrogen, R⁴ is 4-fluorophenyl, R⁵ is 4-fluorophenyl, m is 2, n is 0 and q is 3, is named "1-[4,4-di-(4-fluorophenyl)butyl]-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine"; and

30 the compound of Formula A where R¹ is 2,4-dihydroxyphenyl, R² is methyl, R³ is hydrogen, R⁴ is phenyl, R⁵ is phenyl, m is 3, n is 0 and q is 0, is named "1-diphenylmethyl-4-[(2-(2,4-dihydroxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]diazepine".

Compounds of the invention where R³ is lower alkyl or hydroxy, and/or where R⁴ and R⁵ are different will have one or two chiral centers and may display optical activity. The optical isomers may be separated using conventional methods. For purposes of the present invention, any compound having optical activity shall include each individual isomer as well as mixtures thereof.

35 As used herein, the term "alkyl" means a branched or unbranched saturated hydrocarbon radical having from 1 to 6 carbon atoms. Examples include methyl, ethyl, n-propyl, iso-propyl, n-butyl, t-butyl, n-pentyl, iso-pentyl, n-hexyl, and the like.

As used herein, the term "alkoxy" means the group -OR wherein R is alkyl as defined above. Examples include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, t-butoxy, n-pentyloxy, n-hexyloxy, and the like.

40 As used herein, the term "lower" modifies alkyl and alkoxy and refers to those radicals having four carbon atoms or less.

As used herein, the term "halo" means fluoro, chloro, bromo and/or iodo.

As used herein, the term "aryl" refers to phenyl and optionally mono-, di-, and tri-substituted phenyl, wherein the optional substituents are lower alkyl, lower alkoxy, hydroxy, trifluoromethyl, or halo. Examples 45 include 3-chlorophenyl, 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,4-dimethoxyphenyl, 4-hydroxyphenyl, 4-methylphenyl, 3-t-butylphenyl, 4-hexylphenyl, and the like.

As used herein, the term "treatment" or "treating" means any treatment of a disease in a mammal, and includes:

- (i) preventing the disease, i.e., causing the clinical symptoms of the disease not to develop;
- 50 (ii) inhibiting the disease, i.e., arresting the development of clinical symptoms; and/or
- (iii) relieving the disease, i.e., causing the regression of clinical symptoms.

As used herein, the terms "pharmaceutically acceptable salts" refers to those salts that retain biological effectiveness and properties of the neutral parent compounds and which are not biologically or otherwise undesirable. Pharmaceutically acceptable acid addition salts may be formed with inorganic acids, such as 55 hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and with organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malic acid, malonic acid, succinic acid, maleic acid, fumaric acid, tartaric acid, citric acid, lactic acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, para-toluenesulfonic acid, salicylic acid, and the

like. The salts may be single or multiple salts of one or more anions, e.g., the mono-, di-, or tri- salts from the above-described acids.

Presently Preferred Embodiments

5 Presently preferred embodiments of this invention are compounds of Formula A wherein R¹ is aryl; further preferred are the compounds where R¹ is aryl, m is 2; q is 0; n is 0; R² is methyl; and R³ is hydrogen. The pharmaceutically acceptable salts of these compounds are also preferred, especially the mono-, di- and tri-hydrochlorides, fumarates, and lactates.

10 Particularly preferred are those compounds where R¹ is 4-methylphenyl or phenyl and R⁴ and R⁵ are the same, e.g., both phenyl, i.e., 1-(diphenylmethyl)-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-methyl]piperazine and 1-(diphenylmethyl)-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine and the trihydrochloride or trilactate salts thereof.

15 Other preferred compounds include those where R¹ is aryl; especially those where R³ is lower alkyl, particularly methyl and isopropyl; m is 2; q is 0; n is 0; and R¹, R⁴ and R⁵ are all phenyl.

Still other preferred compounds include those where q is 3; n is 0; R¹ is phenyl; R³ hydrogen; and R⁴ and R⁵ are both 4-fluorophenyl.

Another preferred compound is that wherein m is 3; q is 0; n is 0; R¹ is phenyl; R² is methyl; R³ is hydrogen; and R⁴ and R⁵ are both phenyl.

20 Utility and Methods of Administration

General Utility

25 The compounds of this invention are useful for treating mammals having a variety of vascular disease states, and have protective activity against some of the deleterious effects resultant upon cerebral ischemia. Disease states that may be treated include stroke, migraine, epilepsy or epileptic psychotic symptoms, hypertension, angina, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse. The compounds of this invention are also useful for treating spinal injuries, and are particularly useful for treating cerebrovascular disease states, for example, stroke.

30 Generally, vascular disease states are found in mammals, including: domestic commercial animals such as horses, cattle, sheep and pigs; domestic house animals such as dogs, cats, and the like; and particularly humans.

Activity Testing

35 Activity testing for treating stroke, migraine, epilepsy or epileptic psychotic symptoms, hypertension, angina, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia, cerebrovascular ischemia induced by cocaine abuse, or spinal injuries can be undertaken in vitro and/or in vivo using assay procedures known in the literature. The following are examples of such assay procedures.

40 Activity for treating vascular disease states can be determined in vitro by determining selective vascular relaxant activity, and in vivo by determining general cardiovascular activity.

45 In vitro calcium antagonistic activity of the compounds of this invention is determined by an assay using rat aortic strip, which is a modification of that described by R. Kent, et al., Federation Proceedings, 40, 724 (1981). Cerebrovascular selectivity of action is determined by comparing potencies on rabbit basilar artery and rabbit ear artery using a modification of the procedure described by R. Towart, et al., Arzneim. Forsh., 32(1), 338-346 (1982).

50 In in vivo protective effects of the compounds of this invention against the deleterious effects of cerebral ischemia are determined by use of the standard gerbil brain ischemia model. This assay is a modification of that described by T. Kirino, Brain Res., 239, 57-69P (1982).

55 General Administration

The compounds of this invention are administered at a therapeutically effective dosage, i.e., a dosage

sufficient to provide treatment for the disease states previously described. Administration of the active compounds and salts described herein can be via any of the accepted modes of administration for agents that serve similar utilities.

Generally, a daily dose is from 0.02 to 50 mg/kg of body weight per day of the active compound of 5 Formula A. Most conditions respond to treatment comprising a dosage level on the order of 0.1 to 4 mg/kilogram of body weight per day. Thus, for administration to a 70 kg person, the dosage range would be about 1.4 to 3500 mg per day, preferably about 7.0 to 280 mg per day.

Depending on the specific disease state, administration can be via any accepted systemic route, for 10 example, via parenteral, oral, intravenous, or nasal routes, in the form of solid, semi-solid or liquid dosage forms, such as for example, tablets, suppositories, pills, capsules, powders, solutions, suspensions, aerosols, emulsions or the like, preferably in unit dosage forms suitable for simple administration of precise dosages. The compositions will include a conventional pharmaceutical carrier or excipient and an active compound of Formula A and, in addition, may include other medicinal agents, pharmaceutical agents, carriers, adjuvants, etc.

15 If desired, the pharmaceutical composition to be administered may also contain minor amounts of non-toxic auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like, such as for example, sodium acetate, sorbitan monolaurate, triethanolamine oleate, etc.

The compounds of this invention are generally administered as a pharmaceutical composition which 20 comprises a pharmaceutical excipient in combination with a compound of Formula A. The level of the drug in a formulation can vary within the full range employed by those skilled in the art, e.g., from about 0.01 weight percent (w%) to about 99.99 w% of the drug based on the total formulation and about 0.01 w% to 99.99 w% excipient.

Oral Administration

25

The preferred manner of administration, for the conditions detailed above, is oral using a convenient daily dosage regimen which can be adjusted according to the degree of affliction. For such oral administration, a pharmaceutically acceptable, non-toxic composition is formed by the incorporation of the compound of formula A in any of the normally employed excipients, such as, for example, pharmaceutical 30 grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, gelatin, sucrose, magnesium carbonate, and the like. Such compositions take the form of solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like. Such compositions may contain between 0.01 wt% and 99.99 wt% of the compound of Formula A, but preferably such compositions will contain between 25 wt% and about 80 wt%.

35

Preferably the compositions will take the form of a pill or tablet and thus the composition will contain, along with the active ingredient, a diluent such as lactose, sucrose, dicalcium phosphate, and the like; a disintegrant such as starch or derivatives thereof; a lubricant such as magnesium stearate and the like; and a binder such as a starch, polyvinylpyrrolidone, gum acacia, gelatin, cellulose and derivatives thereof, and the like.

40

Suppositories

For systemic administration via suppository, traditional binders and carriers include, for example, polyalkaline glycol or triglycerides [e.g., PEG 1000 (96%) and PEG 4000 (4%)]. Such suppositories may be 45 formed from mixtures containing active ingredients in the range of from about 0.5 wt% to about 10 wt%; preferably from about 1 wt% to about 2 wt%.

Liquids

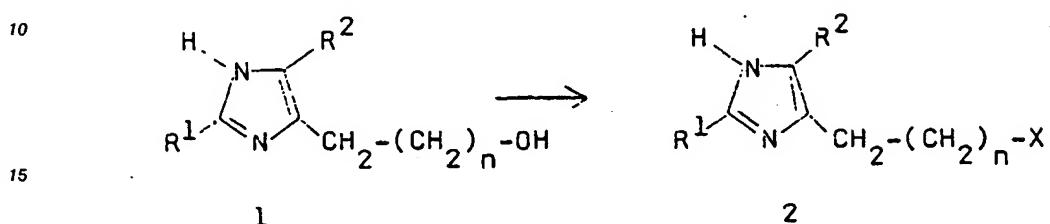
50 Liquid pharmaceutically administerable compositions can, for example, be prepared by dissolving, dispersing, etc. an active compound (about 0.5% to about 20%), as described above, and optional pharmaceutical adjuvants in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol and the like, to thereby form a solution or suspension.

Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in this 55 art; for example, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pennsylvania, 16th Ed., 1980. The composition to be administered will, in any event, contain a quantity of the active compound(s) in a pharmaceutically effective amount for relief of the particular condition being treated in accordance with the teachings of this invention.

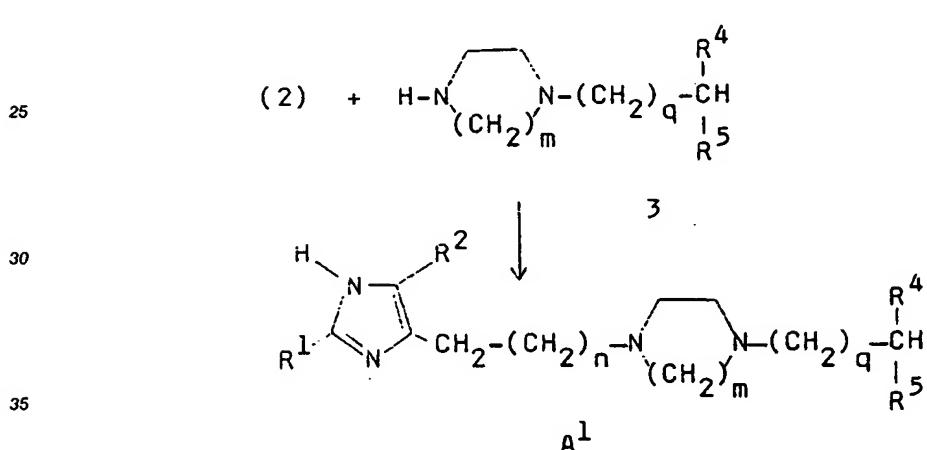
Methods of Preparation

The compounds of this invention can be made as shown in Reaction Schemes I to VI, wherein R¹, R², R³, R⁴, and R⁵ have the same meaning as set forth above in the Summary Of The Invention, and X is halo.

REACTION SCHEME I



Step I-A



Step I-B

I. Preparation of Formula A Where R³ is Hydrogen

Referring to Reaction Scheme I, in Step I-A a mixture of a compound of Formula 1 with an inert hydrocarbon solvent (for example, benzene, toluene, chloroform and the like) is refluxed with a slight excess of a halogenating agent, for example, a thionyl halide (such as thionyl chloride), to produce the corresponding alkyl halide derivative, compound of Formula 2. Compounds of Formula 1 are obtained by reacting the appropriate amidine with the appropriate dione using the procedures of Dziuron and Schunack [Arch. Pharm., 306, 347 (1973) and Arch. Pharm., 307, 46 (1973)] Imbach, et al Bull. Soc. Chim. France, 3 1059 (1971), Cornforth and Huang, J. Chem. Soc., (1948) 731-735, Ewins, J. Chem. Soc., 99 2052 (1911), of U.S. patent 4,107,307. The reaction is conducted at a temperature from about 0°C to the reflux temperature of the solvent, but preferably between about 40°C and 65°C.

In Step I-B, the compound of Formula 2 is condensed with a compound of Formula 3, for example, at a temperature from about 25° to 80° C. preferably at the reflux temperature of the solvent system used.

55 The 1-substituted piperazines of Formula 3 are commercially available or can be made by the procedures of Hamlin, et al., *J. Am. Chem. Soc.*, 71, 2731 (1949) or Cheeseman, *J. Chem. Soc.*, (1975), 115-123. Diazepine analogs (i.e., those compounds where m is 3) can be made by this method using diazepine as the starting material instead of piperazine. An alkaline solution is made by dissolving a compound of

5 Formula 3 in a polar solvent (for example, methanol, ethanol, or a mixture such as ethanol and water, methanol and water, acetone in water, dimethylformamide in water, isopropanol in water, tetrahydrofuran in water; in the ratio of from about 10:90 to about 90:10, preferably about 60:40), and adding a base (such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and the like). The alkaline solution is heated to reflux.

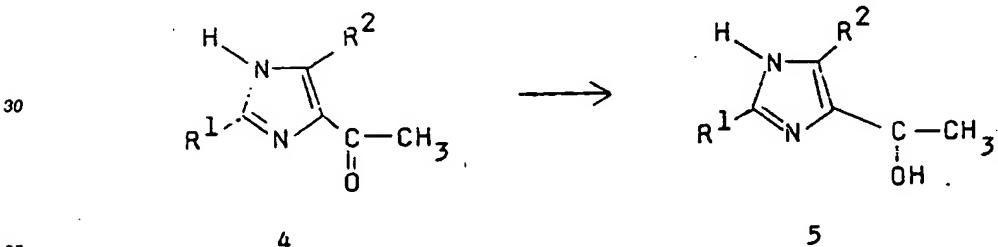
10 A solution of the compound of Formula 2 dissolved in the same polar solvent is added dropwise to the refluxing solution of the compound of Formula 3. After about 1 to 24 hours, preferably about 2 to 5 hours, the condensed product of Formula A¹ is separated from the reaction mixture either by precipitation or evaporation under reduced pressure. The reaction mixture is allowed to stand at room temperature, for example, for about 8 to 24 hours, preferably overnight. If the product precipitated, the resulting crystals are removed by filtration and recrystallized in an alcohol, preferably methanol or ethanol giving the free base of Formula A¹. If the product is an oil, the oil is washed with water and dissolved in diethyl ether. Acid is added and the product is precipitated as the acid addition salt using ethanol.

15 The free base can be converted to the salt by dissolving the free base in a suitable organic solvent, such as ethanol or ether, and extracting with acidic aqueous solution. The use of heat may be required to dissolve the free base, depending upon the acid chosen.

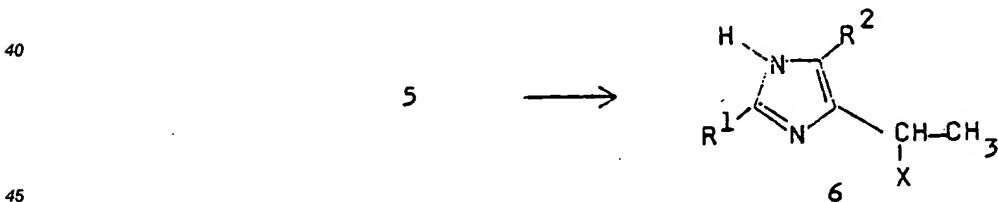
The salt can be converted back to the free base by suspending it, for example in ether, and adding an excess of a dilute aqueous base, such as potassium carbonate, until the salt dissolves. The organic layer is separated, washed with water, dried and evaporated to yield the free base.

20 The salt of a compound of formula A can be converted to another salt by methods known in the art for interconversion of salts.

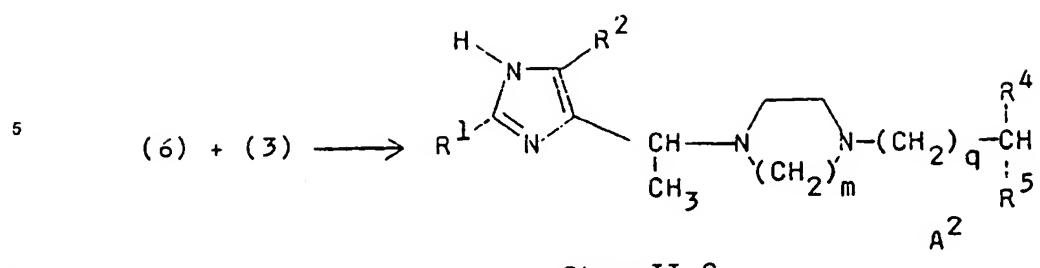
25 REACTION SCHEME II



Step II-A



Step II-B



Step II-C

II. Preparation of Formula A Where R³ is Methyl and n is 0

15 Referring to Reaction Scheme II, in Step II-A a compound of Formula 4 [obtained using the procedure
of Vecchio, et al., Chim. Ind. (Milan), **58**(6), 451 (1976) or of Haruki, et al., Nippon Kagaku Zasshiu, **86**(9),
942-946 (1965) (Japan)] is reduced by contacting it with a reducing agent, such as a hydride (for example,
potassium borohydride, or lithium aluminum hydride) in an alcoholic solution (for example, methanol,
20 ethanol, isopropanol, and the like). The solution is stirred for about 2 to 16 hours, e.g., overnight, and the
resulting solid material, of Formula 5, is removed by filtration (using reduced pressure if necessary),
washed, dried and used in the next step without further purification.

In Step II-B, the crude compound of Formula 5 is dissolved in an inert solvent (for example, chloroform, dichloromethane, benzene, toluene, and the like). A halogenating agent, such as thionyl chloride, is added to the solution and the resulting mixture is heated at reflux for a period of time between 1 and 10 hours, preferably between about 4 and 6 hours. After cooling, the solvent is removed under reduced pressure and the residue is triturated in acetone to give a compound of Formula 6.

30 In Step II-C, the compound of Formula 6 and a compound of Formula 3 are reacted together under the conditions described in Step I-B to give a compound according to Formula A². An oil product may be separated, dissolved in ether, and acidified to precipitate. The reaction time is about 1 to 24 hours, preferably about 4 to 5 hours.

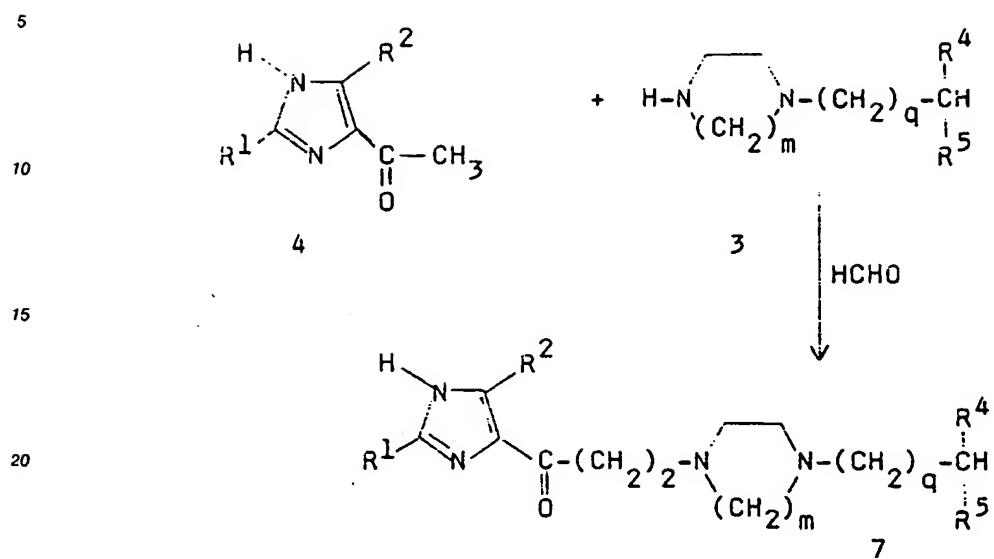
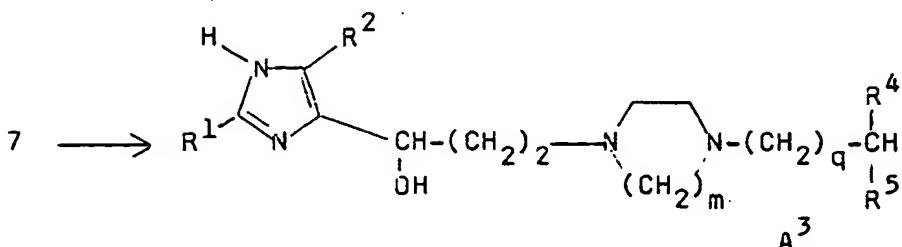
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REACTION SCHEME IIIStep III-AStep III-BIII. Preparation of Formula A Where R³ is Hydroxyl and n is 2

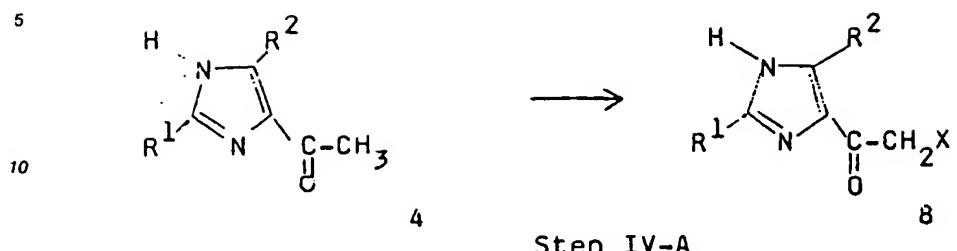
40 Referring to Reaction Scheme III, in Step III-A a methyl ketone, such as a compound of Formula 4, an amine, such as a compound of Formula 3, and formaldehyde are reacted together under the conditions typically used for a Mannich reaction, to give a compound of Formula 7. Thus, the ketone of Formula 7 is dissolved in a solvent such as water, methanol, ethanol, or acetic acid and formaldehyde is introduced. The amine is then added and the reaction mixture is refluxed. If necessary a small amount of an acid such as hydrochloric acid, may be introduced to assure that the reaction mixture is not basic.

45 In Step III-B, the compound of Formula 7 is reduced under conditions similar to those described in Step II-A, to give a compound of Formula A³.

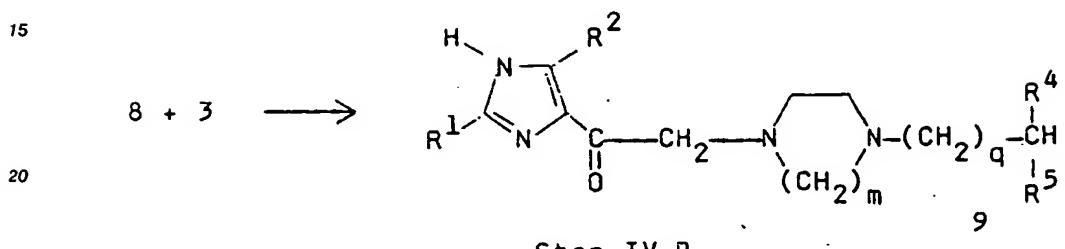
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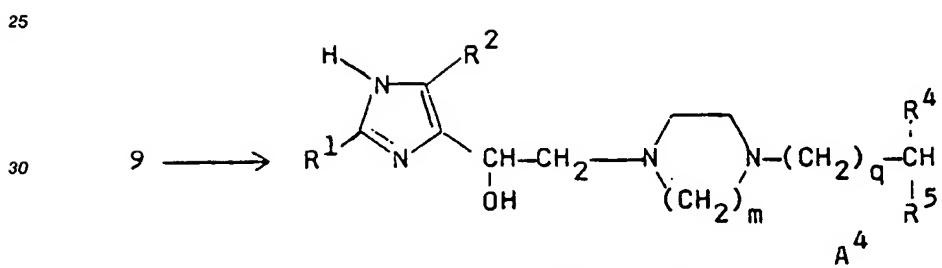
REACTION SCHEME IV



Step IV-A



Step IV-B



Step IV-C

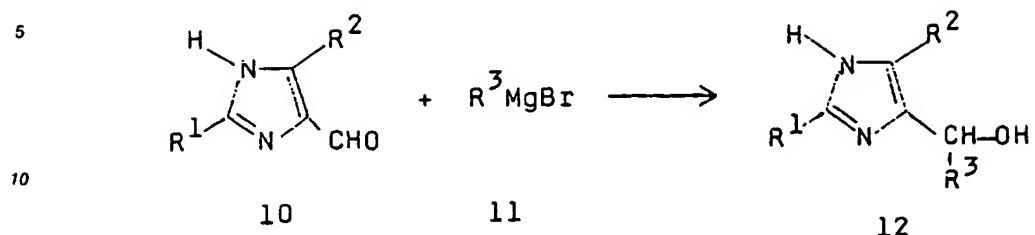
IV. Preparation of Formula A Where R³ is Hydroxyl and n is 1

40 Referring to Reaction Scheme IV, in Step IV-A a compound of Formula 4 is halogenated, by contacting it with a halogenating agent, for example, thionyl halide, under conditions similar to those described in Step I-A, to give a compound of the Formula 8.

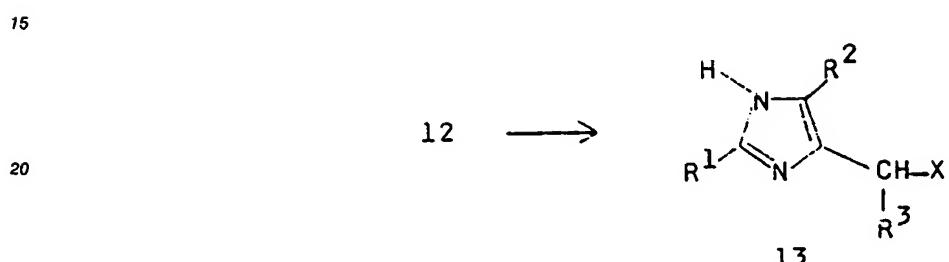
In Step IV-B, a compound of Formula 8 and a compound of Formula 3 are condensed by contacting them under conditions similar to those described for Step I-B, to give a compound of Formula 9.

45 In Step IV-C, a compound of Formula 9 is reduced, by contacting it with a reducing agent under conditions similar to those described for Step II-A to give a compound of Formula A⁴.

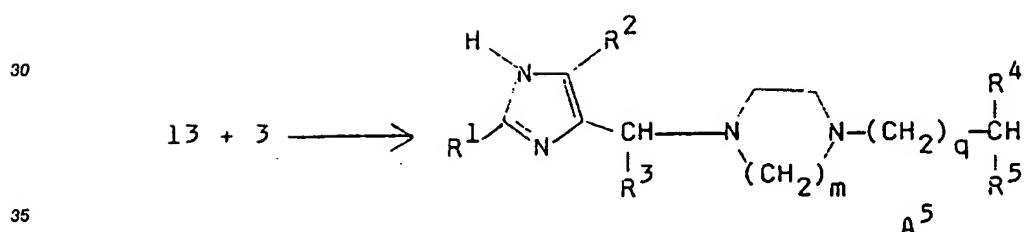
REACTION SCHEME V



Step V-A



Step V-B



Step V-C

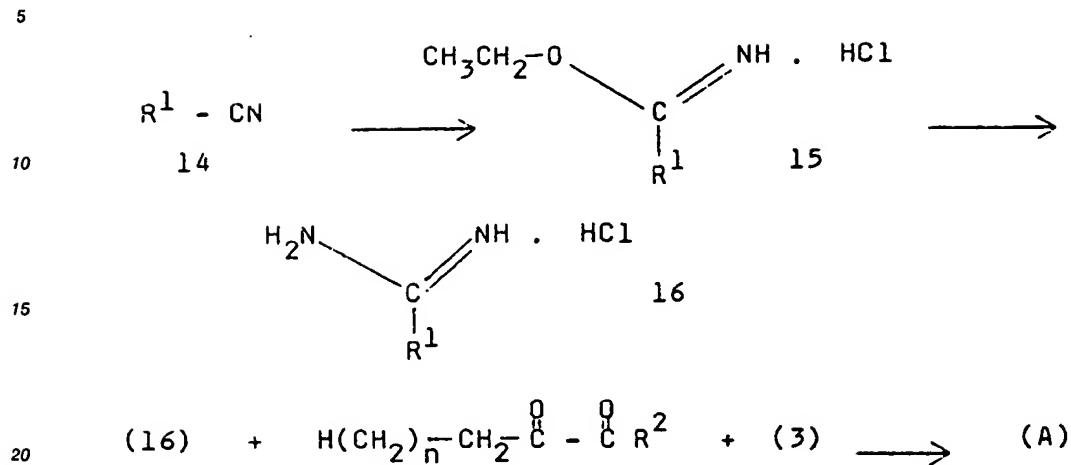
40 V. Preparation of Formula A Where R³ is Lower Alkyl

Referring to Reaction Scheme V, in Step V-A, the Grignard reagent of a lower alkyl halide, the compound of Formula 11, is contacted with an imidazole compound of Formula 10 [obtained using the procedure of Cornforth and Huang, *J. Chem. Soc.*, (1948), 731-735] in a neutral solvent (for example, diethyl ether, tetrahydrofuran, tetrahydropyran, and the like) and refluxed for between 15 minutes and 2 hours, preferably between 20 minutes and 40 minutes, and is then cooled and poured into ice water. The aqueous layer is extracted with a suitable organic solvent, such as diethyl ether. When the solvent is removed under reduced pressure, a residue is formed that can be recrystallized in ethanol yielding a compound of Formula 12.

In Step V-B, a compound of Formula 12 is halogenated under conditions similar to those described for Step I-A, to give a compound of Formula 13.

In Step V-C, a compound of Formula 13 and a compound of Formula 3 are contacted under conditions similar to those described for Step I-B, to give a compound of Formula A⁵.

REACTION SCHEME VI



Referring to Reaction Scheme VI, the nitrile of Formula 14 is dissolved in alcohol, preferably methanol or ethanol, more preferably 99% ethanol, the solution is saturated with dry HCl gas and stirred at room temperature for from 1 to 24 hours, preferably overnight. The precipitate (compound of Formula 15) is filtered, washed and dried. A second crop of precipitate is collected by placing the mother liquors in a freezer overnight, and the precipitate is washed and dried.

Compound of Formula 15 is added slowly with stirring to an alcohol, preferably methanol, which is saturated with ammonia. Once the compound is dissolved, it is stirred at room temperature for from 1 to 24 hours, preferably overnight. The solution is reduced by 2/3 volume under vacuum, then diluted with 3 times its volume with isopropylacetate. The precipitate formed (compound of Formula 16) is filtered and dried.

Compound of Formula 16 is then dissolved in alcohol, preferably methanol or ethanol, more preferably 99% ethanol. Compound of Formula 17 is added dropwise and the reaction mixture refluxed for 1 to 40 hours, preferably 15 to 25 hours, more preferably about 20 hours. The mixture is then cooled to 15 to 40 °C, preferably about 30 °C, compound of Formula 3 is added, then water, a base (such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, and the like, preferably sodium hydroxide) and a metal hydride (such as lithium bromide, potassium bromide, preferably lithium bromide) are added. Any insoluble material is removed by filtration and the solution is refluxed for 1 to 10 hours, preferably 4 to 6 hours. The reaction mixture is cooled and stirred at room temperature for 1 to 24 hours, preferably overnight. The precipitate is filtered, then poured into an alcohol/water mixture (such as methanol/water, ethanol/water, isopropanol/water in a ratio of from 10:90 to about 90:10, preferably 60:40). The solution is warmed to 50 to 80 °C, preferably about 70 °C, for 15 minutes to 4 hours, preferably about 1 hour, then cooled, and the precipitate filtered and dried to yield compound of Formula A.

45 Preferred Processes

The compounds of the present invention can be prepared according to any of the following last steps, in which non-essential substituents are not referenced, but will be apparent from reference to the foregoing reaction schemes:

50 a 4-haloalkyl-1H-imidazole (or a salt thereof) is condensed with a substituted-4-piperazine to give a compound according to Formula A where m is 2;

55 a 4-haloalkyl-1H-imidazole (or a salt thereof) is condensed with a substituted-4-diazepine to give a compound according to Formula A where m is 3;

55 a 4-(1-halo-C₂-C₄-alkyl)-1H-imidazole (or a salt thereof) is condensed with a substituted-4-piperazine to give a compound according to Formula A wherein m is 2, and R³ is lower alkyl;

55 a 4-(1-halo-C₂-C₄-alkyl)-1H-imidazole (or a salt thereof) is condensed with a substituted-4-diazepine to give a compound according to Formula A wherein m is 3, and R³ is lower alkyl;

a 1-substituted-4-[(1H-imidazol-4-yl)-1-oxo-alkyl]piperazine is reduced to give the corresponding compound according to Formula A where m is 2, and R³ is hydroxy;

a 1-substituted-4-[(1H-imidazol-4-yl)-1-oxo-alkyl]diazepine is reduced to give the corresponding compound according to Formula A where m is 3, and R³ is hydroxy;

5 a 2-(aryl)-4-(ω -haloalkyl)-5-alkyl-1H-imidazole (or a salt thereof) is condensed with a diaryl-alkyl-4-piperazine to give a compound according to Formula A where R¹ is aryl, R² is alkyl, R³ is hydrogen, R⁴ and R⁵ are aryl, m is 2, n is 0-2, and q is 0-3;

a substituted amidine is reacted with a substituted dione and a substituted-4-piperazine or a substituted-4-diazepine to give a compound of Formula A;

10 a pharmaceutically acceptable acid is reacted with a compound of Formula A to form the corresponding acid addition salt of Formula A;

a pharmaceutically acceptable acid addition salt of Formula A is converted to another pharmaceutically acceptable acid addition salt of Formula A; or

15 an acid addition salt of Formula A is reacted with a base to form the corresponding free base compound of Formula A.

PREPARATION 1

Preparation of Compound of Formula 1

20 A solution of 1 mole (117.5 g) of tolunitrile in 500 ml absolute ethanol (99%) was saturated with dry HCl gas then kept under stirring at room temperature overnight. A first crop of crystals was collected by filtration then mother liquors were concentrated and placed in a freezer (-18 °C) for 16 hours. A second crop was obtained, giving an overall yield of 80%. Without further purification, the crude product (160 g) was put in 25 200 ml NH₃-saturated methanol, portionwise with stirring. After complete dissolution the reaction medium was left at room temperature overnight then 1/3 of the methanol was removed under reduced pressure. The resulting solution was diluted with 200 ml of isopropyl-acetate and left to crystallize at room temperature for one day. The desired toluanidine hydrochloride was recovered by filtration, dried overnight at 50 °C and used without further purification in the next step (77 g of a white powder, 90% yield).

30 77 g of the above benzamidine hydrochloride were dissolved in 200 ml of water then one equivalent of butanedione was added. The pH was adjusted to 7 with 2N sodium hydroxide and the reaction medium was left for two hours at 0 °C. The white solid formed was filtered off and washed with acetone. The crude product (93 g) was dissolved in 500 ml of 10N HCl then the solution was heated to 100 °C with stirring for 6 hours. After cooling, the white solid formed was recovered by filtration and recrystallized from water to give 35 65 g of 2-(4-methylphenyl)-5-methyl-4-hydroxymethyl-1H-imidazole, melting point, 167-169 °C.

This 4-hydroxymethyl-1H-imidazole was then reacted with a thionyl halide using the procedures set forth above to form the 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride used in Example 1.

40 EXAMPLES

The following examples are given to enable those skilled in the art to more clearly understand and to practice the present invention. They should not be considered as a limitation on the scope of the invention, but merely as being illustrative and representative thereof.

45

EXAMPLE 1

1-Diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine and Derivatives Thereof

50

1A. Formula A Where R¹ is 4-Methylphenyl; R² is Methyl; R³ is Hydrogen; R⁴ and R⁵ are Phenyl; m is 2; n is 0; and q is 0

55 50 Grams (0.2 mol) of 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride dissolved in 200 ml of a mixture of ethanol:water 60:40 were added dropwise to a refluxing solution of 55 grams (0.2 mol) of N-(diphenylmethyl)piperazine and 24 grams (0.6 mol) sodium hydroxide in 200 ml of a mixture of ethanol:water 60:40. After 2 to 3 hours 1-diphenylmethyl-4-[(2-(4-methyl-phenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine precipitated from the reaction mixture. After having left the crystals

standing at room temperature, they were removed by filtration and recrystallized from methanol to give the free base in 70% yield which melted at 220-222 °C.

The free base was converted to its acid addition salt by the process taught in Example 6.

5 1B. Formula A Varying R¹ and R²

Similarly, following the procedure of Part A above, but replacing 2-(4-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride with:

- 2-phenyl-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 10 2-(3-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(2-methylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(4-t-butylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(3-t-butylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(2-t-butylphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 15 2-(4-chlorophenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(3-chlorophenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(2-chlorophenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(4-methoxyphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(3-methoxyphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 20 2-(2-methoxyphenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride;
- 2-(2-methylphenyl)-4-chloromethyl-5-ethyl-1H-imidazole hydrochloride;
- 2-(4-methylphenyl)-4-chloromethyl-5-t-butyl-1H-imidazole hydrochloride;
- 2-(4-methylphenyl)-4-chloromethyl-1H-imidazole hydrochloride;
- 25 2-(3,4-dimethoxyphenyl)-4-bromomethyl-5-methyl-1H-imidazole hydrochloride; and
- 2,5-di-(4-methylphenyl)-4-chloromethyl-1H-imidazole hydrochloride;

there is obtained:

- 1-diphenylmethyl-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 214 °C;
- 1-diphenylmethyl-4-[(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 30 1-diphenylmethyl-4-[(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 216 °C;
- 1-diphenylmethyl-4-[(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 215 °C;
- 1-diphenylmethyl-4-[(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 40 1-diphenylmethyl-4-[(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of about 225 °C;
- 1-diphenylmethyl-4-[(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)methyl]piperazine;
- 45 1-diphenylmethyl-4-[(2-(4-methylphenyl)-1H-imidazol-4-yl)methyl]piperazine;
- 1-diphenylmethyl-4-[(2-(3,4-dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydrochloride salt of which has a melting point of 230 °C; and
- 1-diphenylmethyl-4-[(2,5-di-(4-methylphenyl)-1H-imidazol-4-yl)methyl]piperazine;

50 1C. Formula A Varying q, R⁴ and R⁵

Similarly, following the procedure of Part A above, but replacing N-(diphenylmethyl)piperazine with:

- N-[di-(2-methylphenyl)methyl]piperazine;
- N-[di-(3-methylphenyl)methyl]piperazine;
- 55 N-[di-(4-methylphenyl)methyl]piperazine;
- N-[di-(2-t-butylphenyl)methyl]piperazine;
- N-[di-(3-t-butylphenyl)methyl]piperazine;
- N-[di-(4-t-butylphenyl)methyl]piperazine;

N-[di-(2-methoxyphenyl)methyl]piperazine;
 N-[di-(3-methoxyphenyl)methyl]piperazine;
 N-[di-(4-methoxyphenyl)methyl]piperazine;
 N-[di-(2-chlorophenyl)methyl]piperazine;
 5 N-[di-(3-chlorophenyl)methyl]piperazine;
 N-[di-(4-chlorophenyl)methyl]piperazine;
 N-[di-(4-fluorophenyl)methyl]piperazine;
 N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;
 N-(2,2-diphenylethyl)piperazine;
 10 N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine;

and

N-(4,4-diphenylbutyl)piperazine,

there is obtained:

1-[di-(2-methylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 15 1-[di-(3-methylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(4-methylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(2-t-butylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(3-t-butylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(4-t-butylphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 20 1-[di-(2-methoxyphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(3-methoxyphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(4-methoxyphenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(2-chlorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[di-(3-chlorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 25 1-[di-(4-chlorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the
 trihydrochloride salt of which has a melting point of about 225 °C;
 1-[di-(4-fluorophenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the
 trihydrochloride salt of which has a melting point of about 210 °C;
 1-[1-(4-chlorophenyl)-1-(phenyl)methyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]-
 30 piperazine;
 1-(2,2-diphenylethyl)-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine;
 1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]-
 piperazine; and
 1-(4,4-diphenylbutyl)-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine.

1D. Formula A Varying R¹; R²; R⁴; R⁵ and q

Similarly, by following the procedures of Parts B and C above, other compounds of Formula A where R³ is hydrogen, m is 2, and n is 0 are obtained, such as:

40 1-diphenylmethyl-4-[(2-(3-trifluoromethylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the
 trihydrochloride salt of which has a melting point of about 210 °C;
 1-diphenylmethyl-4-[(2-phenyl-1H-imidazol-4-yl)methyl]piperazine, the fumarate salt of which has a
 melting point of 170 °C;
 1-[di-(4-chlorophenyl)methyl]-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydroch-
 45 loride salt of which has a melting point of 220 °C; and
 1-[4,4-di-(4-fluorophenyl)butyl]-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, the trihydroch-
 loride salt of which has a melting point of 198 °C.

1E. Formula A Varying m

50 Similarly, by following the procedures of Parts A to D above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

For example, substituting 2-phenyl-4-chloromethyl-5-methyl-1H-imidazolehydrochloride for 2-(4-methyl-phenyl)-4-chloromethyl-5-methyl-1H-imidazole hydrochloride, and by substituting diphenylmethyl-4-dia-
 55 zepine for diphenylmethyl-4-piperazine, there is obtained 1-diphenylmethyl-4-[(2-phenyl-5-methyl-1H-im-
 idazol-4-yl)methyl]diazepine, the trihydrochloride salt of which has a melting point of about 205 °C.

EXAMPLE 2

1-Diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine and Derivatives Thereof2A. Formula 5 Where R¹ is Phenyl; and R² is Methyl

5 32 Grams (0.59 mol) of potassium borohydride were added portionwise to a solution of 30 g (0.15 mol) of 2-phenyl-4-acetyl-5-methylimidazole in 1500 ml of MeOH. After stirring overnight, a solid material was removed by filtration, then the solvent was evaporated under reduced pressure to give 27 g of 2-phenyl-4-(1-hydroxyethyl)-5-methylimidazole. The crude compound thus isolated was used without further purification.

10 2B. Formula 6 Where R¹ is Phenyl; R² is Methyl; and X is Chloro

15 27 Grams (0.13 mol) of 2-phenyl-4-(1-hydroxyethyl)-5-methylimidazole were dissolved in 700 ml of chloroform with 44 ml (0.6 mol) of thionyl chloride and refluxed for 5 hours. After cooling, the mixture was evaporated, the residue triturated in acetone, thereby giving, in approximately stoichiometric yield, 2-phenyl-4-(1-chloroethyl)-5-methylimidazole hydrochloride, m.p. 190 °C.

20 2C. Formula 6 Varying R¹, R², and the Length of Alkyl at Position 4 of the Imidazole

20 Similarly, following the procedures of Part A and B above, but replacing 2-phenyl-4-acetyl-5-methylimidazole with:

25 2-(phenyl)-4-(2-methylpropanoyl)-5-methylimidazole;
 2-(3-methylphenyl)-4-acetyl-5-methylimidazole;
 2-(2-methylphenyl)-4-acetyl-5-methylimidazole;
 2-(4-t-butylphenyl)-4-acetyl-5-methylimidazole;
 2-(3-t-butylphenyl)-4-acetyl-5-methylimidazole;
 2-(2-t-butylphenyl)-4-acetyl-5-methylimidazole;
 2-(4-chlorophenyl)-4-acetyl-5-methylimidazole;
 2-(3-chlorophenyl)-4-acetyl-5-methylimidazole;
 30 2-(2-chlorophenyl)-4-acetyl-5-methylimidazole;
 2-(4-methoxyphenyl)-4-acetyl-5-methylimidazole;
 2-(3-methoxyphenyl)-4-acetyl-5-methylimidazole;
 2-(2-methoxyphenyl)-4-acetyl-5-methylimidazole;
 2-(2-methylphenyl)-4-acetyl-5-ethylimidazole;
 35 2-(4-methylphenyl)-4-acetyl-5-t-butylimidazole; and
 2-(4-methylphenyl)-4-acetylimidazole,

there is obtained:

40 2-(phenyl)-4-(1-chloro-2-methylpropyl)-5-methylimidazole hydrochloride;
 2-(3-methylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-methylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(4-t-butylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(3-t-butylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-t-butylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(4-chlorophenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 45 2-(3-chlorophenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-chlorophenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(4-methoxyphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(3-methoxyphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-methoxyphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 50 2-(2-methylphenyl)-4-(1-chloroethyl)-5-ethylimidazole hydrochloride;
 2-(4-methylphenyl)-4-(1-chloroethyl)-5-t-butylimidazole hydrochloride; and
 2-(4-methylphenyl)-4-(1-chloroethyl)-imidazole hydrochloride.

2D. Formula A Where R¹ is Phenyl; R² is Methyl; R³ is Methyl; R⁴ and R⁵ are Phenyl; m is 2; n is 0; and q is 0

55 14 Grams (0.052 mol) of N-(diphenylmethyl)piperazine and 6 grams (0.15 mol) of sodium hydroxide were dissolved in 180 ml of a mixture of ethanol:water 60:40. The mixture was heated to reflux, then 2-

phenyl-4-(1-chloroethyl)-5-methylimidazole hydrochloride in 180 milliliters of ethanol:water 60:40 were added dropwise. After 4 to 5 hours under reflux, the reaction mixture was allowed to cool to room temperature. The oil that separated was washed twice with water, then dissolved in ether and hydrochloric acid was added. The precipitate was recrystallized from ethanol to give 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride (55% yield), which melted at 215°C.

2E. Formula A Where R³ is Methyl; R⁴ and R⁵ are Phenyl; m is 2; n is 0; q is 0; and Varying R¹ and R²

Similarly, following the procedure of Part D above, but replacing 2-phenyl-4-(1-chloroethyl)-5-methylimidazole hydrochloride with:

10 2-(phenyl)-4-(1-chloro-2-methylpropyl)-5-methylimidazole hydrochloride;
 2-(phenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(3-methylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-methylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 15 2-(4-t-butylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(3-t-butylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-t-butylphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(4-chlorophenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(3-chlorophenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 20 2-(2-chlorophenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(4-methoxyphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(3-methoxyphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 2-(2-methoxyphenyl)-4-(1-chloroethyl)-5-methylimidazole hydrochloride;
 25 2-(2-methylphenyl)-4-(1-chloroethyl)-5-ethylimidazole hydrochloride;
 2-(4-methylphenyl)-4-(1-chloroethyl)-5-t-butylimidazole hydrochloride; and
 2-(4-methylphenyl)-4-(1-chloroethyl)-imidazole hydrochloride,

there is obtained:

10 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine hydrochloride;
 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 15 1-diphenylmethyl-4-[1-(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 25 and 1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride.

2F. Formula A Where R¹ is Phenyl; R² is Methyl; R³ is Methyl; m is 2; n is 0; and Varying q, R⁴ and R⁵

Similarly, following the procedure of Part D above, but replacing N-(diphenylmethyl)piperazine with:

10 N-[di-(2-methylphenyl)methyl]piperazine;
 N-[di-(3-methylphenyl)methyl]piperazine;
 N-[di-(4-methylphenyl)methyl]piperazine;
 N-[di-(2-t-butylphenyl)methyl]piperazine;
 N-[di-(3-t-butylphenyl)methyl]piperazine;
 N-[di-(4-t-butylphenyl)methyl]piperazine;
 15 N-[di-(2-methoxyphenyl)methyl]piperazine;
 N-[di-(3-methoxyphenyl)methyl]piperazine;
 N-[di-(4-methoxyphenyl)methyl]piperazine;
 N-[di-(2-chlorophenyl)methyl]piperazine;

N-[di-(3-chlorophenyl)methyl]piperazine;
 N-[di-(4-chlorophenyl)methyl]piperazine;
 N-[di-(4-fluorophenyl)methyl]piperazine;
 5 N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;
 N-(2,2-diphenylethyl)piperazine;
 N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine;
 and
 N-(4,4-diphenylbutyl)piperazine,
 there is obtained:
 10 1-[di-(2-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(3-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(4-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(2-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(3-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 15 1-[di-(4-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(2-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(3-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 20 1-[di-(4-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(2-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(3-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 25 1-[di-(4-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[di-(4-fluorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[4-chlorophenyl]-1-(phenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 trihydrochloride;
 1-(2,2-diphenylethyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;
 1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine
 30 trihydrochloride; and
 1-(4,4-diphenylbutyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride.

2G. Formula A Where R³ is Methyl; m is 2; n is 0; and Varying R¹; R²; R⁴; R⁵ and q

35 Similarly, by following the procedures of Parts E and F above, other compounds of Formula A where R³ is methyl, m is 2, and n is 0 are obtained, such as:
 1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-(4-methylphenyl)-1H-imidazol-4-yl)ethyl]-
 piperazine trihydrochloride; and
 1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[1-(2-(3-methoxyphenyl)-5-propyl-1H-imidazol-4-yl)ethyl]-
 40 piperazine trihydrochloride.

2H. Formula A Where R³ is Lower Alkyl Other Than Methyl

45 Similarly, following the procedure of Part D above, but replacing 2-phenyl-4-(1-chloroethyl)-5-methylimidazole hydrochloride with:
 2-phenyl-4-(1-chloropropyl)-5-methylimidazole hydrochloride; and
 2-phenyl-4-(1-chlorobutyl)-5-methylimidazole hydrochloride,
 there is obtained:
 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride; and
 50 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)butyl]piperazine trihydrochloride.

2I. Formula A Varying m

55 Similarly, by following the procedures of Parts A-H above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

EXAMPLE 3

1-Diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride and Derivatives Thereof

3A. Formula 9 Where R¹ is Phenyl; R² is Methyl; R⁴ and R⁵ are Phenyl; m is 2; and q is 0

5

10 Grams (0.036 mol) of 2-phenyl-4-(2-bromoethanoyl)-5-methyl-1H-imidazole and 8.5 grams (0.034 mol) of N-(diphenylmethyl)piperazine and 5 grams (0.036 mol) of potassium carbonate were added to 300 ml of ethanol. The mixture was refluxed under stirring overnight. After cooling, the salts were removed by filtration and the solvent was removed under reduced pressure. The residue was extracted by dichloromethane and washed twice with water. The organic layer was dried over sodium sulfate and evaporated. Trituration of the residue with ethanol gave a white precipitate, 1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-oxoethyl]piperazine, which was used in the next reaction step without further purification.

3B. TriHCl Salt of Formula A Where R¹ is Phenyl; R² is Methyl; R³ is Hydroxy; R⁴ and R⁵ are Phenyl; m is 2; n is 1; and q is 0

6 Grams of 1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-oxoethyl]piperazine was dissolved in 100 ml of methanol. The reaction was cooled to 5°C and then 2 grams (0.05 mol) of sodium borohydride was added portionwise. After stirring for 2 hours at room temperature, the mixture was evaporated off. The residue was extracted with dichloromethane and washed with water. Then the organic layer was dried over sodium sulphate and the solvent removed under reduced pressure. The crude material was then dissolved in diethyloxide and hydrochloric acid was added. The white precipitate was then removed by filtration and dried to give 1-diphenylmethyl-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride, which melted at 200°C.

25

3C: TriHCl Salt of Formula A Where R³ is Hydroxy; R⁴ and R⁵ are Phenyl; m is 2; n is 1; q is 0; and Varying R¹ and R²

Similarly, following the procedures of Parts A and B above, but replacing 2-phenyl-4-(2-bromoethanoyl)-5-methyl-1H-imidazole with:

2-(3-methylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(2-methylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(4-t-butylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(3-t-butylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(2-t-butylphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(4-chlorophenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(3-chlorophenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(2-chlorophenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(4-methoxyphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(3-methoxyphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(2-methoxyphenyl)-4-(2-bromoethanoyl)-5-methyl-1H-imidazole;
 2-(2-methylphenyl)-4-(2-bromoethanoyl)-5-ethyl-1H-imidazole;
 2-(4-methylphenyl)-4-(2-bromoethanoyl)-5-t-butyl-1H-imidazole; and
 2-(4-methylphenyl)-4-(2-bromoethanoyl)-1H-imidazole, there is obtained:
 1-diphenylmethyl-4-[2-(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[2-(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[2-(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[2-(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[2-(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[2-(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[2-(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl]-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

5 1-diphenylmethyl-4-[2-(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

10 1-diphenylmethyl-4-[2-(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[2-(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

15 1-diphenylmethyl-4-[2-(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride; and

1-diphenylmethyl-4-[2-(2-(4-methylphenyl)-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride.

15 3D. TriHCl Salt of Formula A Where R¹ is Phenyl; R² is Methyl; R³ is Hydroxy; m is 2; n is 1; q is 0; and Varying R⁴ and R⁵

Similarly, following the procedures of Parts A and B above, but replacing N-(diphenylmethyl)piperazine with:

20 N-[di-(2-methylphenyl)methyl]piperazine;

N-[di-(3-methylphenyl)methyl]piperazine;

N-[di-(4-methylphenyl)methyl]piperazine;

N-[di-(2-t-butylphenyl)methyl]piperazine;

N-[di-(3-t-butylphenyl)methyl]piperazine;

25 N-[di-(4-t-butylphenyl)methyl]piperazine;

N-[di-(2-methoxyphenyl)methyl]piperazine;

N-[di-(3-methoxyphenyl)methyl]piperazine;

N-[di-(4-methoxyphenyl)methyl]piperazine;

N-[di-(2-chlorophenyl)methyl]piperazine;

30 N-[di-(3-chlorophenyl)methyl]piperazine;

N-[di-(4-chlorophenyl)methyl]piperazine;

N-[di-(4-fluorophenyl)methyl]piperazine;

N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;

N-(2,2-diphenylethyl)piperazine;

35 N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine; and

N-(4,4-diphenylbutyl)piperazine, there is obtained:

1-[di-(2-methylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(3-methylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

40 1-[di-(4-methylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(2-t-butylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

45 1-[di-(3-t-butylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(4-t-butylphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

50 1-[di-(2-methoxyphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(3-methoxyphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

55 1-[di-(4-methoxyphenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(2-chlorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(3-chlorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

1-[di-(4-chlorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 1-[di-(4-fluorophenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 5 1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]-piperazine trihydrochloride;
 1-(2,2-diphenylethyl)-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;
 10 1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]-piperazine trihydrochloride; and
 1-(4,4-diphenylbutyl)-4-[2-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride.

3E. TriHCl Salt of Formula A Where R³ is Hydroxy; m is 2; n is 1 or 2; and Varying R¹; R²; R⁴; R⁵ and q

15 Similarly, by following the procedures of Parts C and D above, other compounds of Formula A where R³ is hydroxy, m is 2, and n is 1 or 2 are obtained, such as:
 1-[(4-chlorophenyl)-1-(phenyl)methyl]-4-[3-(2-phenyl-5-methyl-1H-imidazol-4-yl)-3-hydroxypropyl]-piperazine trihydrochloride, by starting with 2-phenyl-4-(3-bromopropanoyl)-5-methyl-1H-imidazole in part 20 3A; and
 1-(2,2-diphenylethyl)-4-[2-(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-hydroxyethyl]piperazine trihydrochloride;

3F. Formula A Varying m

25 Similarly, by following the procedures of Parts A-E above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

EXAMPLE 4

30 1-Diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine and Derivatives Thereof

4A. Formula 12 Where R¹ is Phenyl; R² is Methyl; and R³ is Isopropyl

35 35 Grams (0.45 mol) of 2-chloropropane was added to 10.8 g (0.45 mol) of magnesium in 100 ml of diethyl ether. Then 55.8 g (0.3 mol) of 2-phenyl-4-formyl-5-methyl-1H-imidazole in 100 ml of THF were added. At the end of the addition, the mixture was refluxed for 30 minutes and then cooled and poured on ice water. The aqueous layer was extracted twice with 100 ml of diethyl ether. Evaporation of the solvent gave a residue which was recrystallized in ethanol to yield 40 grams (58% yield) of 2-phenyl-4-(1-hydroxy-2-methylpropyl)-5-methyl-1H-imidazole, which melted at 214°C.

4B. Formula 12 Where R⁶ is Isopropyl; and Varying R¹ and R²

45 Similarly, following the procedure of Part A above, but replacing 2-phenyl-4-formyl-5-methyl-1H-imidazole with:

2-(3-methylphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(2-methylphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(4-t-butylphenyl)-5-methyl-4-formyl-1H-imidazole;
 50 2-(3-t-butylphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(2-t-butylphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(4-chlorophenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(3-chlorophenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(2-chlorophenyl)-5-methyl-4-formyl-1H-imidazole;
 55 2-(4-methoxyphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(3-methoxyphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(2-methoxyphenyl)-5-methyl-4-formyl-1H-imidazole;
 2-(2-methylphenyl)-5-ethyl-4-formyl-1H-imidazole;

2-(4-methylphenyl)-5-t-butyl-4-formyl-1H-imidazole;
 2-(4-methylphenyl)-4-formyl-1H-imidazole;
 2-(3,4-dimethoxyphenyl)-4-formyl-5-methyl-1H-imidazole; and
 2,5-di-(4-methylphenyl)-4-formyl-1H-imidazole, there is obtained:
 5 2-(3-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(4-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(3-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 10 2-(4-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(3-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(4-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 15 2-(3-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-methylphenyl)-5-ethyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(4-methylphenyl)-5-t-butyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 20 2-(3,4-dimethoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole; and
 2,5-di-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole.

4C. Formula 13 Where R¹ is Phenyl; R² is Methyl; R³ is Isopropyl; and X is Chloro

27 g of 2-phenyl-4-(1-hydroxy-2-methylpropyl)-5-methyl-1H-imidazole are dissolved in 700 ml of chloroform with 44 ml of thionyl chloride (SOCl₂) and refluxed for 5 hours. 2-Phenyl-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride is isolated in quantitative yield.

4D. Formula 13 Where R⁶ is Isopropyl; X is Chloro; and Varying R¹ and R²

30 Similarly, following the procedure of Part C above, but replacing 2-phenyl-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole with:
 2-(3-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-methylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(4-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 35 2-(3-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-t-butylphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(4-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(3-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-chlorophenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 40 2-(4-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(3-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-methoxyphenyl)-5-methyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 2-(2-methylphenyl)-5-ethyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole;
 45 2-(4-methylphenyl)-5-t-butyl-4-(1-hydroxy-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3,4-dimethoxyphenyl)-4-(1-hydroxy-2-methylpropyl)-5-methyl-1H-imidazole; and
 2,5-di-(4-methylphenyl)-4-(1-hydroxy-2-methylpropyl)-1H-imidazole,
 there is obtained:
 2-(3-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 50 2-(2-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 55 2-(4-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;

2-(2-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-methylphenyl)-5-ethyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-methylphenyl)-5-t-butyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 5 2-(3,4-dimethoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride; and
 2,5-di-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride.

4E. TriHCl Salt of Formula A Where R¹ is Phenyl; R² is Methyl; R³ is Isopropyl; R⁴ and R⁵ are Phenyl; m is 2; n is 0; and q is 0

10 14 Grams (0.05 mol) of diphenylmethyl-4-piperazine and 6 grams (0.15 mol) of sodium hydroxide are dissolved in 180 ml of a mixture of ethanol:water 60:40. The mixture is heated to reflux, then 2-phenyl-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride in 180 milliliters of ethanol:water 60:40 are added dropwise. After 4 to 5 hours under reflux, the reaction mixture is allowed to cool to room temperature. The oil that separated is washed twice with water, then dissolved in ether and hydrochloric acid is added. The precipitate is recrystallized from ethanol to give 1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride.

20 4F. TriHCl Salt of Formula A Where R³ is Isopropyl; R⁴ and R⁵ are Phenyl; m is 2; n is 0; q is 0; and Varying R¹ and R²

Similarly, following the procedure of Part E above, but replacing 2-phenyl-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride with:

25 2-(3-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-methylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-t-butylphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 30 2-(4-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-chlorophenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(4-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 35 2-(3-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-methoxyphenyl)-5-methyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(2-methylphenyl)-5-ethyl-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 40 4-(1-chloro-2-methylpropyl)-5-t-butyl-1H-imidazole hydrochloride;
 2-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride;
 2-(3,4-dimethoxyphenyl)-4-(1-chloro-2-methylpropyl)-5-methyl-1H-imidazole hydrochloride; and
 2,5-di-(4-methylphenyl)-4-(1-chloro-2-methylpropyl)-1H-imidazole hydrochloride,

40 there is obtained:
 1-diphenylmethyl-4-[1-(2-(3-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 45 1-diphenylmethyl-4-[1-(2-(4-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(3-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(2-t-butylphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 50 50 1-diphenylmethyl-4-[1-(2-(4-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(3-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 55 55 1-diphenylmethyl-4-[1-(2-(2-chlorophenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;
 1-diphenylmethyl-4-[1-(2-(4-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(3-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(2-methoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

5 1-diphenylmethyl-4-[1-(2-(2-methylphenyl)-5-ethyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

10 1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-5-t-butyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

10 1-diphenylmethyl-4-[1-(2-(3,4-dimethoxyphenyl)-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride; and

1-diphenylmethyl-4-[1-(2,5-di-(4-methylphenyl)-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride.

15 4G. Formula A Where R³ is Isopropyl, Varying q, R⁴ and R⁵

Similarly, following the procedure of Part E above, but replacing N-(diphenylmethyl)piperazine with:

N-[di-(2-methylphenyl)methyl]piperazine;

N-[di-(3-methylphenyl)methyl]piperazine;

20 N-[di-(4-methylphenyl)methyl]piperazine;

N-[di-(2-t-butylphenyl)methyl]piperazine;

N-[di-(3-t-butylphenyl)methyl]piperazine;

N-[di-(4-t-butylphenyl)methyl]piperazine;

N-[di-(2-methoxyphenyl)methyl]piperazine;

25 N-[di-(3-methoxyphenyl)methyl]piperazine;

N-[di-(4-methoxyphenyl)methyl]piperazine;

N-[di-(2-chlorophenyl)methyl]piperazine;

N-[di-(3-chlorophenyl)methyl]piperazine;

N-[di-(4-chlorophenyl)methyl]piperazine;

30 N-[di-(4-fluorophenyl)methyl]piperazine;

N-[1-(4-chlorophenyl)-1-(phenyl)methyl]piperazine;

N-(2,2-diphenylethyl)piperazine;

N-[3-(phenyl)-3-(4-methoxyphenyl)propyl]piperazine; and

N-(4,4-diphenylbutyl)piperazine,

35 there is obtained:

1-[di-(2-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(3-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

40 1-[di-(4-methylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(2-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(3-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine

45 trihydrochloride;

1-[di-(4-t-butylphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(2-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

50 1-[di-(3-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(4-methoxyphenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(2-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine

55 trihydrochloride;

1-[di-(3-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[di-(4-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine

10 1-[di-(4-chlorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine

trihydrochloride;

1-[di-(4-fluorophenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[1-(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]-

5 piperazine trihydrochloride;

1-(2,2-diphenylethyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride;

1-[3-(phenyl)-3-(4-methoxyphenyl)propyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]-piperazine trihydrochloride; and

10 1-(4,4-diphenylbutyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylpropyl]piperazine trihydrochloride.

4H. TriHCl Salt of Formula A Where R³ is Lower Alkyl Other Than Isopropyl

15 Similarly, by following the procedures of Parts A to G above, and substituting in for 2-chloropropane in Part A the following compounds:

1-chloroethane;

chloromethane;

2-chlorobutane,

20 there are obtained the corresponding compounds where R³ is, respectively, ethyl, methyl and butyl, such as:

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)ethyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylbutyl]piperazine trihydrochloride;

25 1-(4,4-diphenylbutyl)-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)-2-methylbutyl]piperazine trihydrochloride;

1-[1-(4-chlorophenyl)-1-(phenyl)methyl]-4-[1-(2-phenyl-5-methyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride;

1-diphenylmethyl-4-[1-(2-(4-methylphenyl)-5-ethyl-1H-imidazol-4-yl)propyl]piperazine trihydrochloride;

30 and 1-diphenylmethyl-4-[1-(2,5-diphenyl-1H-imidazol-4-yl)-2-methylbutyl]piperazine trihydrochloride.

4I. Formula A Varying m

35 Similarly, by following the procedures of Parts A-H above, but replacing the piperazines there-used with the corresponding diazepines, the compounds of Formula A wherein m is 3 are obtained.

EXAMPLE 5

40 1-Diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine and Derivatives Thereof

A. A solution of 4-methylbenzonitrile in 99% ethanol was saturated with 3 equivalents of dry HCl gas and the reaction mixture was stirred overnight. The precipitate which formed was filtered and the mother liquors were placed in a freezer at -18°C overnight. A second crop was obtained from the mother liquors. The combined crops were dried at 30°C overnight under vacuum, giving 78% yield of ethyl 4-methylbenzenecarboximidate hydrochloride (compound of Formula 15).

B. The product of step A was added portionwise with stirring to methanol which had been saturated with ammonia in the ratio of 1 liter methanol to 1 kilogram of product of step A. The product of step A dissolved slowly and the solution was stirred overnight. Two thirds of the volume was evaporated under vacuum. The remaining solution was diluted with three times its volume of isopropylacetate. The solution was filtered and dried overnight at 50°C to yield 4-methylbenzenecarboximidamide hydrochloride (compound of Formula 16) in 90% yield.

C. One mole of the product of step B was dissolved in 2 liters of 99% ethanol. 1.1 moles of butanedione were added dropwise, the solution was warmed to reflux and refluxed for 20 hours. The solution was allowed to cool to 30°C and 1 mole of powdered biphenylpiperazine was added portionwise. This was followed by the addition of 1 liter of water, 1.5 equivalents of sodium hydroxide (as 12N solution), and 1.1 equivalents of lithium bromide. The solution was filtered to remove insolubles and then refluxed for 5

hours. The solution was allowed to cool to room temperature and was stirred overnight. The precipitate which formed was filtered and the filter cake was added to an ethanol:water mixture (60:40) in the ratio of 3 liters of solvent mixture to 1 kilogram of filter cake. The solution was warmed to 70°C for one hour and then allowed to cool to room temperature. The precipitate formed was filtered and dried overnight at 5 80°C under vacuum to form 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine in 88% yield.

D. The trihydrochloride salt of the free base of the product of step C was formed by dissolving the free base of step C in 99% ethanol at the ratio of 1.1 liter of ethanol per mole of product. One mole of 1N HCl solution was slowly added. The solution was filtered and then warmed to 60°C. With slow addition, 10 250 ml of 12N HCl solution were added. The solution was slowly cooled to -10°C and the precipitate was filtered off and dried under vacuum at 100°C for 48 hours to yield 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine trichydrochloride, m.p. 204-205°C.

EXAMPLE 6

15

Conversion of Free Compound To Salt

Trihydrochloride salt -

20 The hydrochloride salt was obtained by addition of hydrochloric acid to the free base of a compound of Formula A dissolved in ethanol or ether. See step D of Example 5.

Monohydrochloride salt -

25 100 g. of 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine were dissolved in 300 ml of ethanol at 95°C. To this solution 1 equivalent of 1N HCl was added with stirring. The reaction mixture was stirred at room temperature for 2 hours then the solvents were evaporated off under reduced pressure. The residue was dissolved in ether and the precipitate was filtered. The precipitate was recrystallized from isopropyl ether:acetone (1:1) to yield 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-30 1H-imidazol-4-yl)methyl]piperazine monohydrochloride, m.p. 186-188°C with decomposition.

Monomaleate Salt -

35 5 g. (0.0115 mole) of 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine were dissolved in 300 ml of ethanol at 95°C. To this solution 1.34 g (0.0115 mole) of maleic acid was added with stirring. The reaction mixture was stirred at room temperature for 2 hours then the solvents were evaporated off under reduced pressure. The residue was dissolved in ether and the precipitate was filtered. The precipitate was recrystallized from isopropyl ether:acetone (1:1) to yield 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-40 1H-imidazol-4-yl)methyl]piperazine monomaleate, m.p. 164-166°C with decomposition.

Trifumarate salt -

45 To 5 g. of 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine (0.0115 mole) in acetone (100 ml) there was added 1.33 g. (0.0115 mole) of fumaric acid. The solution was heated to reflux, allowed to cool to room temperature, and allowed to stand at room temperature until precipitate formed. The precipitate was collected by filtration and recrystallized from ethanol to give the fumarate salt of 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, m.p. 195°C in almost quantitative yield.

50 In a similar manner, all compounds of Formula A in free base form can be converted to the acid addition salts by treatment with the appropriate acid, for example, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, malic acid, maleic acid, tartaric acid, citric acid, lactic acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluene-sulfonic acid, and the like.

55

EXAMPLE 7

Conversion of Salt to Free Base

5 20 g. of 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine trihydrochloride were solubilized in 200 ml of water. Sodium hydroxide (5N) was added dropwise with stirring until pH 8-9. The aqueous medium was extracted twice by 200 ml of dichloromethane. The organic phases were combined then washed with cold water until neutrality. Sodium sulfate was added to dry the organic phase, then the solvent was evaporated under reduced pressure. The resulting residue was crystallized from aqueous ethanol (90%) to give 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine.

10 If desired, the extraction phase can be eliminated to allow direct recovery of the product followed by recrystallization.

10

EXAMPLE 8

Conversion of one Salt to Another Salt

15 5 g of 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine monofumarate were dissolved in 100 ml of hot ethanol. 3 ml of commercial concentrated HCl solution (10N) were added with stirring. The solution was refluxed for 30 minutes then the solution was allowed to cool to room temperature. The solvent was evaporated off and the residue was crystallized twice from ethanol at 98°C to yield 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine trihydrochloride, m.p. 202-204° with decomposition.

EXAMPLES 9-15

20 The following examples illustrate the preparation of representative pharmaceutical formulations containing an active compound of Formula A, e.g., 1-diphenylmethyl-4-[2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride. Other compounds and salts of Formula A, such as those prepared in accordance with Examples 1-8, can be used as the active compound in the formulations of Examples 9-15.

EXAMPLE 9

30

I.V. Formulation		
35	Active compound	0.14 g
	Propylene glycol	20.0 g
	POLYETHYLENE GLYCOL 400	20.0 g
	TWEEN 80	1.0 g
	0.9% Saline solution	100.0 ml

40 Other compounds of Formula A and the pharmaceutically acceptable salts thereof may be substituted therein.

EXAMPLE 10

45

Ingredients	Quantity per tablet, mgs.	
50	Active compound	25
	cornstarch	20
	lactose, spray-dried	153
	magnesium stearate	2

55 The above ingredients are thoroughly mixed and pressed into single scored tablets.

EXAMPLE 11

EP 0 289 227 B1

5

Ingredients	Quantity per capsule, mgs.
Active compound	100
lactose, spray-dried	148
magnesium stearate	2

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

10 EXAMPLE 12

15

Ingredients	Quantity per tablet, mgs.
Active compound	1
cornstarch	50
lactose	145
magnesium stearate	5

20

The above ingredients are mixed intimately and pressed into single scored tablets.

25 EXAMPLE 13

30

Ingredients	Quantity per capsule, mgs.
Active compound	150
lactose	92

The above ingredients are mixed and introduced into a hard-shell gelatin capsule.

35 EXAMPLE 14

An injectable preparation buffered to a pH of 7 is prepared having the following composition:

40

Ingredients	
Active compound	0.2 g
KH ₂ PO ₄ buffer (0.4 M solution)	2 ml
KOH (1 N)	q.s. to pH 7
water (distilled, sterile)	q.s. to 20 ml

45

EXAMPLE 15

50 An oral suspension is prepared having the following composition:

55

Ingredients	
Active compound	0.1 g
fumaric acid	0.5 g
sodium chloride	2.0 g
methyl paraben	0.1 g
granulated sugar	25.5 g
sorbitol (70% solution)	12.85 g
Veegum K (Vanderbilt Co.)	1.0 g
flavoring	0.035 ml
colorings	0.5 mg
distilled water	q.s. to 100 ml

15 EXAMPLE 16

Ischemia (Stroke, Epilepsy)

A. Five minute model of bilateral common carotid artery occlusion in the gerbil with 72 hour survival

20 1) Normal animals - Using the procedure of Kirino Brain Res., 239, 57 (1982), microscopic sections (8 mm) of brain tissue were obtained and stained with cresyl fast violet and haematoxylin-eosin. Abnormal brain cells were counted and expressed as a percentage of the total area counted using the procedure of Alps, et al, Br. J. Pharmacol. Proc. Suppl., 88, 250P (1986). The findings for 10 animals with 100 microscopic fields counted were: mean % abnormal neurones = 4.54 ±0.44%.

25 2) Sham-operated animals - The animals were anesthetized with a halothane-nitrous oxide-oxygen mixture. (Halothane was initially 5% then reduced to 1.5%. The gases were delivered via face mask.) Carotid arteries were surgically exposed (no ischemia) and survival time was 72 hours post-surgery. The microscopic sections were prepared and counted as in 1) above. In this case 7 animals were used and 100 microscopic fields were counted. The results were: mean % abnormal neurones = 4.61 ±0.31%.

30 3) Untreated ischemic controls - In this case animals were subjected to 5 minute bilateral carotid artery occlusion with 72 hour survival. The microscopic sections were prepared and counted as in 1) above. In this case 12 animals were used and 120 microscopic fields were counted. The results were: mean % abnormal neurones = 78.30 ±2.94%.

35 4) Parenteral, 15 minute pre-ischemia treated - The animals were given 500 mg/kg i.p. of 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]piperazine trihydrochloride 15 minutes prior to ischaemic insult. The treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 10 animals were used and 100 microscopic fields were counted. The results were: mean % abnormal neurones = 26.90 ±3.30%.

40 5) Parenteral 15 minute pre-ischemic treated - The animals were given 250 mg/kg i.p. of 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]piperazine trihydrochloride 15 minutes prior to ischaemic insult. Treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 6 animals were used and 60 microscopic fields were counted. The results were: mean % abnormal neurones = 27.20 ±4.30%.

45 6) Parenteral 15 minute post-ischemia treated - The animals were given 500 mg/kg i.p. of 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]piperazine trihydrochloride 15 minutes after ischaemic insult. The treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 9 animals were used and 90 microscopic fields were counted. The results were: mean % abnormal neurones = 41.70 ±4.60%.

50 7) Oral, pre-ischemia treated - The animals were given 5 mg/kg p.o. b.i.d. of 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]piperazine trihydrochloride for 3 days and on the 4th day at 1 hour pre-ischaemic. Treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 11 animals were used and 110 microscopic fields were counted. The results were: mean % abnormal neurones = 3.00 ±1.00%.

55 8) Oral, pre-ischemia treated - The animals were given 10 mg/kg p.o. of 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]piperazine trihydrochloride for 3 days and on 4th day at 1 hour pre-ischaemia. Treatment was repeated b.i.d. for 72 hours. The microscopic sections were prepared and counted as in 1) above. In this case 9 animals were used and 90 microscopic fields

were counted. The results were: mean % abnormal neurones = $22.00 \pm 3.10\%$.

B. Ten minute Model of four vessel occlusion with 72 hour survival.

The procedure used was that of Alps, et al., *Neurology*, 37, 809 (1987). The object of this assay was to count abnormally appearing cells in 7 different areas and exymers as a percentage of the total area counted. The number of counts per structure depended upon size, e.g., cortical areas had double the number of other areas. Mean whole brain scores were also determined for percent abnormalities. Normal brains were also used to account for incidence of artifact changes attributed to the fixation process.

1) Normal animals - Under pentobarbital anesthesia samples were obtained, fixed with 10% buffered formal gab and microscopic samples were prepared as described in A above. In this case 6 animals were used with the results shown in the below table.

Brain Area	Mean % Abnormal Neurones	No. Fields Counted
Hip CA ₁	$1.45 \pm 0.40\%$	60
Hip CA ₂₋₅	$0.43 \pm 0.20\%$	60
Hip Cortex	$2.90 \pm 0.64\%$	120
Striatum	$5.80 \pm 0.54\%$	60
Str. Cortex	$3.22 \pm 0.70\%$	120
Thalamus	$4.38 \pm 0.92\%$	60
Purk. cells	$5.61 \pm 1.88\%$	60
Mean Brain score	$3.33 \pm 0.33\%$	540
Mean score per area	$3.39 \pm 0.76\%$	7

2) Untreated (saline) ischemic controls - The animals were subjected to 10 minutes of bilateral common carotid artery occlusion (with previously surgically sealed vertebral arteries) with 72 hours survival. The microscopic sections were prepared as in 1) above. In this case 11 animals were used with the results shown in the below table.

Brain Area	Mean % Abnormal Neurones	No. Fields Counted
Hip CA ₁	$71.60 \pm 3.00\%$	110
Hip CA ₂₋₅	$23.80 \pm 2.70\%$	110
Hip. Cortex	$48.50 \pm 2.20\%$	220
Striatum	$45.10 \pm 2.60\%$	110
Str. Cortex	$42.50 \pm 2.10\%$	220
Thalamus	$35.30 \pm 2.00\%$	110
Purk. cells	$32.10 \pm 3.40\%$	110
Mean score per area	$42.70 \pm 5.80\%$	7

Parenteral, post-ischaemia treated - The animals were given 100 mg/kg i.a. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride 5 minutes post-ischaemia plus 500 mg/kg i.p. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine trihydrochloride 15 minutes post-ischaemia. The microscopic sections were prepared according to 1) above. In this case 5 animals were used with the results shown in the below table.

Brain Area	Mean % Abnormal Neurones	No. Fields Counted
Hip CA ₁	$16.76 \pm 4.00\%$	50
Hip CA ₂₋₅	$1.78 \pm 0.99\%$	50
Hip. Cortex	$2.41 \pm 0.30\%$	100
Striatum	$1.54 \pm 0.33\%$	50
Str. Cortex	$2.01 \pm 0.29\%$	100
Thalamus	$0.64 \pm 0.25\%$	50
Purk. cells	$2.22 \pm 0.79\%$	50

C. The effect of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]piperazine

trihydrochloride on pentylenetetrazole-induced seizures and mortality in the mouse.

The procedure used was that described in Allely, and Alps, Br. J. Pharmacol. Proc. Suppl., 92, 605P (1987). Groups of 20 or more (see n in table) male CD-1 mice were predosed with 500 mg/kg i.p. of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]piperazine trihydrochloride at one of three dosing schedules - A (15 minutes), B (60 minutes), or C (3 days b.i.d. plus 15 minutes on 4th day) - before challenging with 100 mg/kg of pentylenetetrazole s.c. The animals were then observed for a 30 minute period and the occurrence of clonic or tonic seizures or death noted. Statistical analysis was by a Chi squared test of association. Results compared against saline treated animals are shown in the below table.

10

	Predose Schedule	Predosed mg/kg i.p.	n	% clonic seizures	% tonic seizures	% death
<hr/>						
15	<u>Saline</u>	--	--	40	92.5	80.0
<hr/>						
20	<u>Drug</u>	A	500	20	85.0	85.0
		B	500	25	88.0	64.0
25		C	500	24	66.7	41.7
						50.0
						36.0
						45.0

In an oral dose ranging study in rats of 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]-piperazine trihydrochloride no death or clinical signs of toxicity were seen at up to 25 mg/kg/day.

30 EXAMPLE 17

Diuresis

Male normotensive rats weighing 290-380 g were divided into four groups of seven animals. All animals were fasted and deprived of water overnight. The following morning, each group of rats was hydrated with deionized water (20 mg/kg.p.o.) 45 minutes prior to the administration of vehicle (1% polysorbate 80 in deionized water) or 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride at doses of 5, 15, or 30 mg/kg p.o. Fifteen minutes post-drug, the animals were saline loaded (30 ml/kg, p.o. 0.9% sodium chloride) and placed individually in metabolism cages. Urine was collected at 1, 3, and 6 hour intervals post-dose. Urine volumes were measured and sodium and potassium levels were determined by flame photometry. Differences between control and treated values were evaluated by one way analysis of variance. 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)-methyl]-piperazine trihydrochloride (30 mg/kg, p.o.) produced significant ($p < .05$) diuresis which was observed at 1 hour and 6 hours post-drug. The compound (30 mg/kg, p.o.) elicited a significant natriuretic effect at the 3 and 6 hour time periods. No significant kaliuretic effects were observed following compound administration.

50

Cumulative time	Urine Volume (ml)			
	control vehicle*	5 mg/kg p.o.	15 mg/kg p.o.	30 mg/kg p.o.
1 hour	3.3 ±2.7	5.7 ±2.5	5.7 ±4.4	6.5 ±2.3
3 hours	7.3 ±3.3	9.5 ±3.6	9.8 ±3.2	10.5 ±2.5
6 hours	9.6 ±3.9	11.8 ±3.9	11.7 ±3.3	14.6 ±1.4

55

Cumulative time	Sodium ion (mEq)			
	control vehicle*	5 mg/kg p.o.	15 mg/kg p.o.	30 mg/kg p.o.
5	1 hour	.06 ±.08	.07 ±.06	.12 ±.16
	3 hours	.28 ±.31	.39 ±.25	.44 ±.20
	6 hours	.55 ±.44	.73 ±.32	.68 ±.28
				1.48 ±.24

Cumulative time	Potassium ion (mEq)			
	control vehicle*	5 mg/kg p.o.	15 mg/kg p.o.	30 mg/kg p.o.
10	1 hour	.03 ±.03	.04 ±.03	.04 ±.05
15	3 hours	.13 ±.09	.16 ±.09	.12 ±.06
	6 hours	.22 ±.12	.26 ±.12	.20 ±.08
				.27 ±.06

EXAMPLE 18

20 Irritable Bowel Syndrome

The test used is a modification of the method of Macht and Barba-Gose, *J. Amer. Pharm. Assoc.*, 20, 558 (1931), which traces the transit of a charcoal meal through the intestine as an index of transit time. In 25 the present model, intestinal transit in conscious mice (15-20 g) was accelerated with an oral dose of barium chloride (300 mg/kg) administered at the same time as the charcoal meal. The animals were sacrificed 10 minutes later and the distance travelled by the charcoal measured. 1-diphenyl-methyl-4-[(2-(4-methylphenyl)-5-methylimidazol-4-yl)methyl]-piperazine trihydrochloride was given as a 15 minute oral pre-treatment and its effect on non-stimulated or barium-stimulated intestinal transit of the charcoal meal was 30 calculated. The results were expressed as inhibition percentage of the total transit induced by Ba^{+2} , and not as the inhibition percentage of the portion representing the Ba^{+2} effect and are shown in the below table.

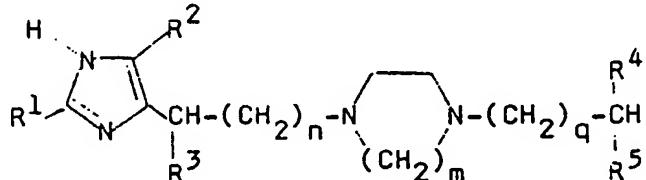
Dose 15 min mg/kg p.o.	% Change Ba^{+2}	% Inhibition of Ba^{+2} effect	% Inhibition Normal Transit
5	+ 93 %	+ 14 %	- 19.3 %
25	+ 93 %	- 30.4 %	- 28.7 %
60	+ 93 %	- 31.7 %	- 16.1 %

40

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

45 1. A compound having the structure represented by the formula:



55

wherein:

 R^1 is aryl; R^2 is aryl, C_{1-4} alkyl, or hydrogen;

5 R³ is C₁-₄ alkyl, hydroxy, or hydrogen;
 R⁴ is aryl;
 R⁵ is aryl;
 m is two or three;
 n is zero, one or two,
 provided that when R³ is hydroxy, n is one or two; and
 q is zero, one, two, or three;
 or a pharmaceutically acceptable salt thereof.

10 2. A compound of Claim 1 wherein m is two, q is zero, n is zero, and R² is methyl.

3. A compound of Claim 2 wherein R³ is hydrogen.

4. A compound of Claim 1 wherein R³ is lower alkyl or hydroxy.

15 5. A compound of Claim 3 wherein R¹ is 4-methylphenyl.

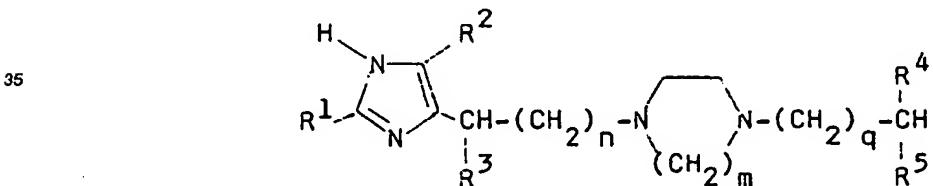
6. A compound of Claim 5 wherein R⁴ and R⁵ are 4-chlorophenyl or 4-fluorophenyl.

20 7. A compound of Claim 2 wherein R¹ is 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,4-dimethoxyphenyl, 3-chlorophenyl, or phenyl.

8. A compound of Claim 1 wherein m is 3.

25 9. A compound selected from 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, 1-diphenylmethyl-4-[2-phenyl-1H-imidazol-4-yl)methyl]piperazine, 1-diphenylmethyl-4-[2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, and pharmaceutically acceptable acid addition salts thereof.

30 10. A compound having the structure represented by the formula:



wherein:

45 R¹ is aryl;
 R² is aryl or C₁-₄ alkyl;
 R³ is C₁-₄ alkyl, hydroxy, or hydrogen;
 R⁴ is aryl;
 R⁵ is aryl;
 m is two or three;
 n is zero, one or two,
 provided that when R³ is hydroxy, n is one or two; and
 q is zero, one, two, or three;
 or a pharmaceutically acceptable salt thereof.

50 11. Use of a compound of any one of the preceding claims in the preparation of a medicament for treating stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombosis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, or spinal injury.

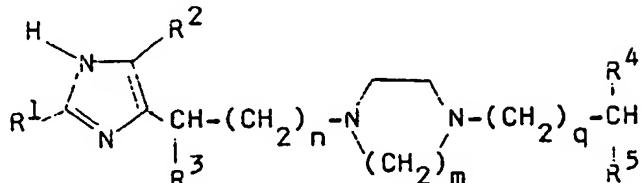
12. A compound of any one of claims 1 to 10 for pharmaceutical use.

13. A pharmaceutical formulation comprising a compound of any one of claims 1 to 10 and a pharmaceutically acceptable excipient.

5

14. A process for the preparation of a compound of formula A

10



15

FORMULA A

wherein:

20

R¹ is aryl;

R² is aryl, lower alkyl, or hydrogen;

R³ is lower alkyl, hydroxy, or hydrogen;

R⁴ is aryl;

R⁵ is aryl;

25

m is two or three;

n is zero, one or two,

provided that when R³ is hydroxy, n is one or two; and

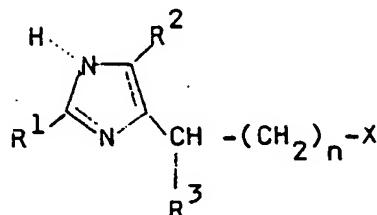
q is zero, one, two, or three;

and the pharmaceutically acceptable salts thereof, which comprises

30

(a) condensing a compound of the formula

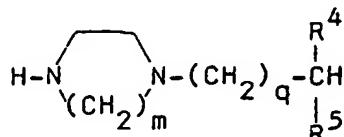
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wherein n, R¹ and R² are as defined above, R³ is hydrogen or lower alkyl, and X is a halogen atom, with a compound of the formula

45

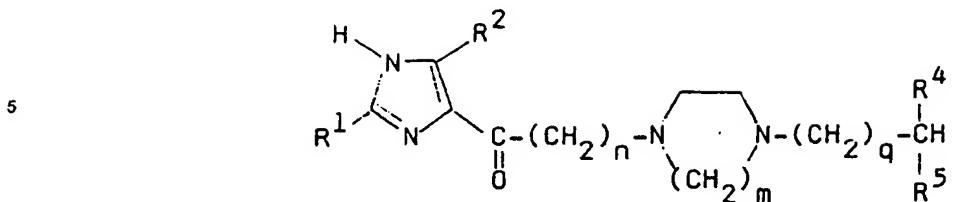


50

wherein m, q, R⁴ and R⁵ are as defined above; or

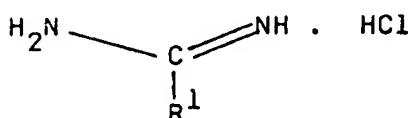
b) reducing a compound of the formula

55



10 wherein R¹, R², R⁴, R⁵, m, and q are as defined above and n is one or two, to form a compound of formula A wherein R³ is hydroxy; or
c) reacting a compound of the formula

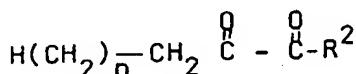
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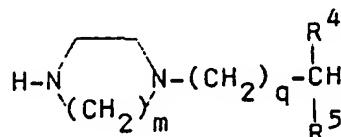
wherein R¹ is as defined above, with a compound of the formula

25



30

35



wherein m, q, R⁴ and R⁵ are as defined above, to form a compound of Formula A wherein R³ is hydrogen; or
40 d) converting a free base compound of formula A to its acid addition salt; or
e) converting an acid addition salt of a compound of formula A to a free base compound of formula A; or
f) converting an acid addition salt of a compound of formula A to another acid addition salt of a compound of formula A.

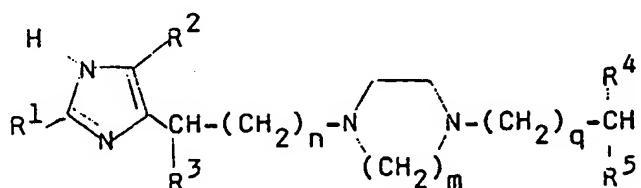
45

Claims for the following Contracting States : ES, GR

1. A process which comprises the preparation of a compound having the structure represented by the formula:

50

55



wherein:

5 R^1 is aryl;
 R^2 is aryl, C_{1-4} alkyl, or hydrogen;
 R^3 is C_{1-4} alkyl, hydroxy, or hydrogen;
 R^4 is aryl;
 R^5 is aryl;
 m is two or three;
 n is zero, one or two,
 provided that when R^3 is hydroxy, n is one or two; and
 10 q is zero, one, two, or three;
 or a pharmaceutically acceptable salt thereof.

2. A process of Claim 1 wherein m is two, q is zero, n is zero, and R^2 is methyl.

15 3. A process of Claim 2 wherein R^3 is hydrogen.

4. A process of Claim 1 wherein R^3 is lower alkyl or hydroxy.

5. A process of Claim 3 wherein R^1 is 4-methylphenyl.

20 6. A process of Claim 5 wherein R^4 and R^5 are 4-chlorophenyl or 4-fluorophenyl.

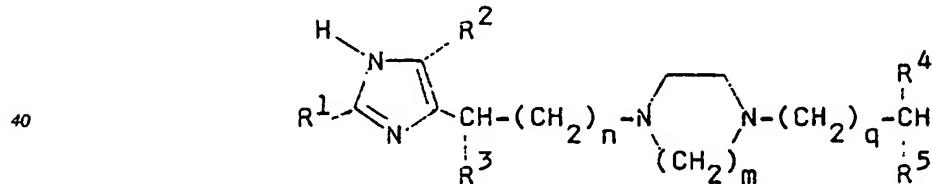
7. A process of Claim 2 wherein R^1 is 3-trifluoromethylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 3,4-dimethoxyphenyl, 3-chlorophenyl, or phenyl.

25 8. A process of Claim 1 wherein m is 3.

9. A process which comprises the preparation of a compound selected from 1-diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazine, 1-diphenylmethyl-4-[2-phenyl-1H-imidazol-4-yl)methyl]piperazine, 1-diphenylmethyl-4-[2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazine, and pharmaceutically acceptable acid addition salts thereof.

30 10. A process which comprises the preparation of a compound having the structure represented by the formula:

35



45 wherein:

46 R^1 is aryl;
 R^2 is aryl or C_{1-4} alkyl;
 R^3 is C_{1-4} alkyl, hydroxy, or hydrogen;
 R^4 is aryl;
 R^5 is aryl;
 m is two or three;
 n is zero, one or two,
 provided that when R^3 is hydroxy, n is one or two; and
 q is zero, one, two, or three;
 55 or a pharmaceutically acceptable salt thereof.

11. Use of a compound of any one of the preceding claims in the preparation of a medicament for treating stroke, epilepsy or epileptic psychotic symptoms, hypertension, angina, migraine, arrhythmia, thrombo-

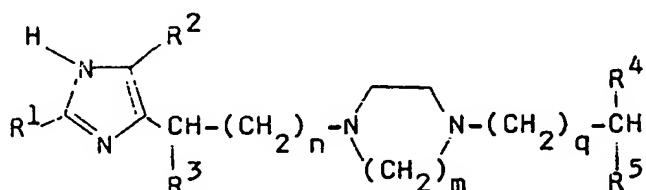
sis, embolism, acute cardiac failure, irritable bowel syndrome, neurodegenerative diseases such as Alzheimer's or Huntington's chorea, diuresis, ischemia such as focal and global ischemia or cerebrovascular ischemia induced by cocaine abuse, or spinal injury.

5 12. A process which comprises the preparation of a pharmaceutical formulation comprising a compound of any one of claims 1 to 10 and a pharmaceutically acceptable excipient.

13. A process for the preparation of a compound of formula A

10

15



FORMULA A

20

wherein:

R¹ is aryl;

R² is aryl, lower alkyl, or hydrogen;

R³ is lower alkyl, hydroxy, or hydrogen;

25 R⁴ is aryl;

R⁵ is aryl;

m is two or three;

n is zero, one or two,

provided that when R³ is hydroxy, n is one or two; and

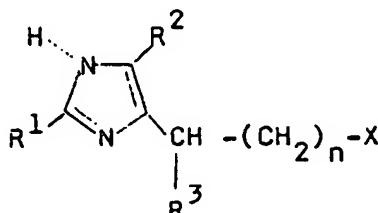
30 q is zero, one, two, or three;

and the pharmaceutically acceptable salts thereof, which comprises

(a) condensing a compound of the formula

35

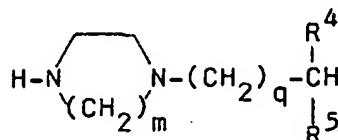
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45

wherein n, R¹ and R² are as defined above, R³ is hydrogen or lower alkyl, and X is a halogen atom, with a compound of the formula

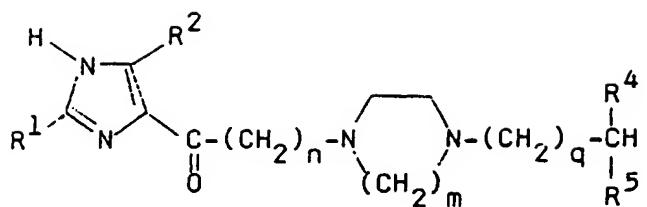
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wherein m, q, R⁴ and R⁵ are as defined above; or

b) reducing a compound of the formula

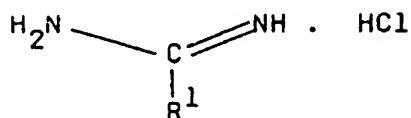


10

wherein R¹, R², R⁴, R⁵, m, and q are as defined above and n is one or two, to form a compound of formula A wherein R³ is hydroxy; or

c) reacting a compound of the formula

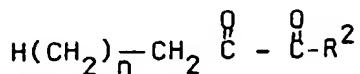
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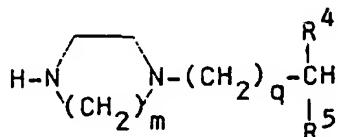
wherein R¹ is as defined above, with a compound of the formula

25



wherein n and R² are as defined above, and a compound of the formula

30



35

wherein m, q, R⁴ and R⁵ are as defined above, to form a compound of Formula A wherein R³ is hydrogen; or

d) converting a free base compound of formula A to its acid addition salt; or

40

e) converting an acid addition salt of a compound of formula A to a free base compound of formula A; or

f) converting an acid addition salt of a compound of formula A to another acid addition salt of a compound of formula A.

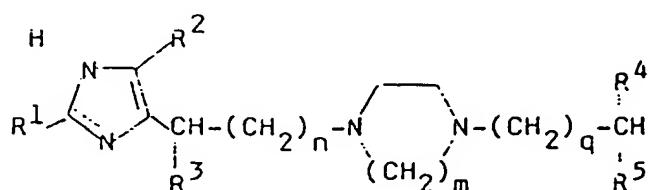
45 **Revendications**

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de structure représentée par la formule :

50

55



dans laquelle

R¹ est un groupe aryle ;
 R² est un groupe aryle, alkyle en C₁ à C₄ ou l'hydrogène ;
 R³ est un groupe alkyle en C₁ à C₄, hydroxy ou l'hydrogène ;
 5 R⁴ est un groupe aryle ;
 R⁵ est un groupe aryle ;
 m a la valeur deux ou trois ;
 n a la valeur zéro, un ou deux,
 sous réserve que lorsque R³ est un groupe hydroxy, n ait la valeur un ou deux ; et
 10 q a la valeur zéro, un, deux ou trois ;
 ou un sel pharmaceutiquement acceptable de ce composé.

2. Composé suivant la revendication 1, dans lequel m est égal à deux, q est égal à zéro, n est égal à zéro et R² est le groupe méthyle.

15 3. Composé suivant la revendication 2, dans lequel R³ est l'hydrogène.

4. Composé suivant la revendication 1, dans lequel R³ est un groupe alkyle inférieur ou hydroxy.

20 5. Composé suivant la revendication 3, dans lequel R¹ est le groupe 4-méthylphényle.

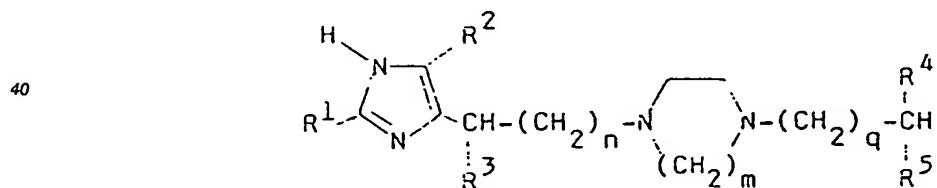
6. Composé suivant la revendication 5, dans lequel R⁴ et R⁵ sont le groupe 4-chlorophényle ou 4-fluorophényle.

25 7. Composé suivant la revendication 2, dans lequel R¹ est le groupe 3-trifluorométhylphényle, 4-méthoxyphényle, 4-chlorophényle, 3,4-diméthoxyphényle, 3-chlorophényle ou phényle.

8. Composé suivant la revendication 1, dans lequel m est égal à 3.

30 9. Composé choisi entre la 1-diphénylméthyl-4-[(2-(4-méthylphényl)-5-méthyl-1H-imidazole-4-yl)méthyl]pipérazine, la 1-diphénylméthyl-4-[(2-phényl-1H-imidazole-4-yl)méthyl]pipérazine, la 1-diphénylméthyl-4-[(2-phényl-5-méthyl-1H-imidazole-4-yl)méthyl]pipérazine et leurs sels d'addition d'acides pharmaceutiquement acceptables.

35 10. Composé ayant la structure représentée par la formule :



dans laquelle

R¹ est un groupe aryle ;
 R² est un groupe aryle ou alkyle en C₁ à C₄ ;
 R³ est un groupe alkyle en C₁ à C₄, hydroxy ou l'hydrogène ;
 50 R⁴ est un groupe aryle ;
 R⁵ est un groupe aryle ;
 m a la valeur deux ou trois ;
 n a la valeur zéro, un ou deux,
 sous réserve que lorsque R³ est un groupe hydroxy, n soit égal à un ou deux ; et
 55 q a la valeur zéro, un, deux ou trois ;
 ou un sel pharmaceutiquement acceptable de ce composé.

11. Utilisation d'un composé suivant l'une quelconque des revendications précédentes dans la préparation

d'un médicament pour le traitement de l'apoplexie, de l'épilepsie ou des syndromes de psychose épileptiques, l'hypertension, l'angor, la migraine, l'arythmie, la thrombose, l'embolie, la crise cardiaque aiguë, le syndrome d'irritation intestinale, des troubles de dégénérescence nerveuse tels que la chorée d'Alzheimer ou d'Huntington, la diurèse, l'ischémie telle que l'ischémie focale et globale ou l'ischémie cérébrovasculaire induite par l'abus de la cocaïne, ou une lésion de la moelle épinière.

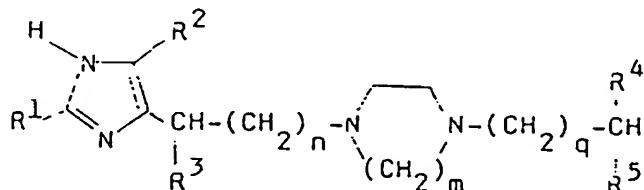
5 12. Composé suivant l'une quelconque des revendications 1 à 10, destiné à un usage pharmaceutique.

10 13. Formulation pharmaceutique, comprenant un composé suivant l'une quelconque des revendications 1 à 10 et un excipient acceptable du point de vue pharmaceutique.

14. Procédé de préparation d'un composé de formule A

15

20



FORMULE A

25

dans laquelle

R¹ est un groupe aryle ;R² est un groupe aryle, alkyle inférieur ou l'hydrogène ;R³ est un groupe alkyle inférieur, hydroxy ou l'hydrogène ;

30

R⁴ est un groupe aryle ;R⁵ est un groupe aryle ;

m a la valeur deux ou trois ;

n a la valeur zéro, un ou deux,

sous réserve que lorsque R³ est un groupe hydroxy, n soit égal à un ou deux ; et

35

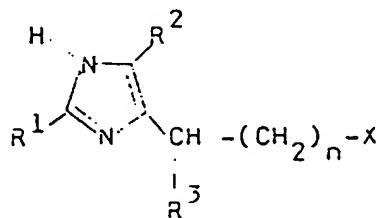
q a la valeur zéro, un, deux ou trois ;

et de ses sels pharmaceutiquement acceptables, qui consiste

(a) à condenser un composé de formule

40

45



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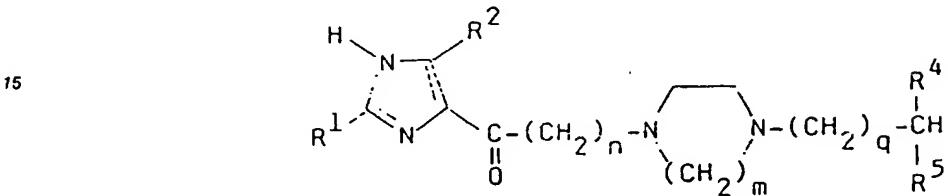
dans laquelle n, R¹ et R² sont tels que définis ci-dessus, R³ est l'hydrogène ou un groupe alkyle inférieur et X est un atome d'halogène,

avec un composé de formule

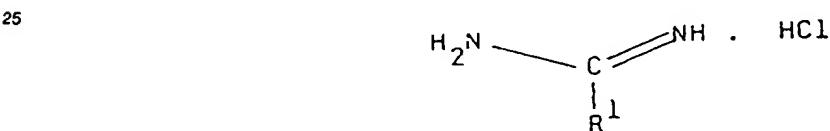
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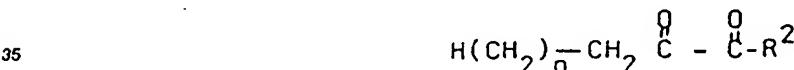
10 dans laquelle m , q , R^4 et R^5 sont tels que définis ci-dessus ; ou bien
b) à réduire un composé de formule



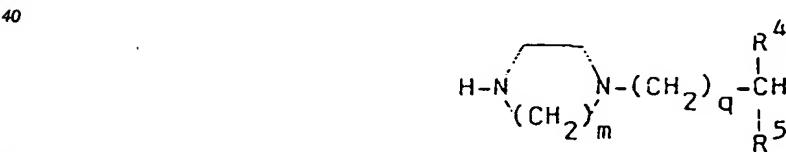
20 dans laquelle R^1 , R^2 , R^4 , R^5 , m et q sont tels que définis ci-dessus et n a la valeur un ou deux,
pour former un composé de formule A dans laquelle R^3 est un groupe hydroxy ; ou bien
c) à faire réagir un composé de formule



30 dans laquelle R^1 est tel que défini ci-dessus, avec un composé de formule



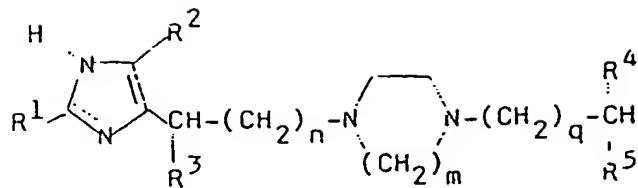
dans laquelle n et R^2 sont tels que définis ci-dessus, et un composé de formule



dans laquelle m , q , R^4 et R^5 sont tels que définis ci-dessus, pour former un composé de formule A
dans laquelle R^3 est l'hydrogène ; ou bien
d) à convertir un composé sous la forme base libre de formule A en son sel d'addition d'acide ; ou
bien
e) à convertir un sel d'addition d'acide d'un composé de formule A en un composé sous la forme
base libre de formule A ; ou bien
f) à convertir un sel d'addition d'acide d'un composé de formule A en un autre sel d'addition d'acide
d'un composé de formule A.

55 Revendications pour les Etats contractants suivants : ES, GR

1. Procédé qui comprend la préparation d'un composé de structure représentée par la formule :



10 dans laquelle :

R¹ est un groupe aryle ;
 R² est un groupe aryle, alkyle en C₁ à C₄ ou l'hydrogène ;
 R³ est un groupe alkyle en C₁ à C₄, hydroxy ou l'hydrogène ;
 R⁴ est un groupe aryle ;

15 R⁵ est un groupe aryle ;
 m a la valeur deux ou trois ;

n a la valeur zéro, un ou deux,

sous réserve que lorsque R³ est un groupe hydroxy, n soit égal à un ou deux ; et
 q a la valeur zéro, un, deux ou trois ;

20 ou d'un sel pharmaceutiquement acceptable de ce composé.

2. Procédé suivant la revendication 1, dans lequel m a la valeur deux, q a la valeur zéro, n a la valeur zéro et R² est un groupe méthyle.

25 3. Procédé suivant la revendication 2, dans lequel R³ est l'hydrogène.

4. Procédé suivant la revendication 1, dans lequel R³ est un groupe alkyle inférieur ou hydroxy.

5. Procédé suivant la revendication 3, dans lequel R¹ est le groupe 4-méthylphényle.

30 6. Procédé suivant la revendication 5, dans lequel R⁴ et R⁵ sont des groupes 4-chlorophényle ou 4-fluorophényle.

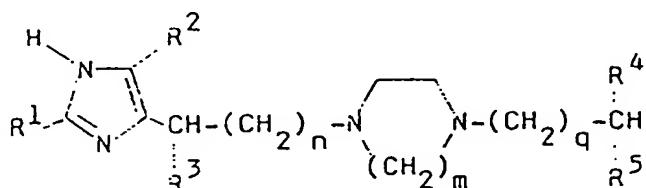
7. Procédé suivant la revendication 2, dans lequel R¹ est un groupe 3-trifluorométhylphényle, 4-méthoxyphényle, 4-chlorophényle, 3,4-diméthoxyphényle, 3-chlorophényle ou phényle.

35 8. Procédé suivant la revendication 1, dans lequel m est égal à 3.

9. Procédé qui comprend la préparation d'un composé choisi entre la 1-diphénylméthyl-4-[(2-(4-méthylphényl)-5-méthyl-1H-imidazole-4-yl)méthyl]pipérazine, la 1-diphénylméthyl-4-[(2-phényl-1H-imidazole-4-yl)méthyl]pipérazine, la 1-diphénylméthyl-4-[(2-phényl-5-méthyl-1H-imidazole-4-yl)méthyl]pipérazine et leurs sels d'addition d'acides pharmaceutiquement acceptables.

40 10. Procédé qui comprend la préparation d'un composé de structure représentée par la formule :

45



55 dans laquelle

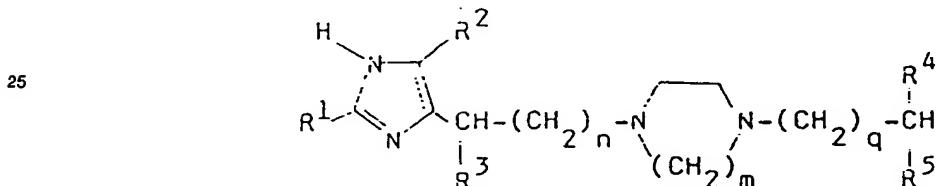
R¹ est un groupe aryle ;
 R² est un groupe aryle ou alkyle en C₁ à C₄ ;
 R³ est un groupe alkyle en C₁ à C₄, hydroxy ou l'hydrogène ;

R⁴ est un groupe aryle ;
 R⁵ est un groupe aryle ;
 m a la valeur deux ou trois ;
 n est égal à zéro, un ou deux,
 5 sous réserve que lorsque R³ est un groupe hydroxy, n soit égal à un ou deux ; et
 q a la valeur zéro, un, deux ou trois ;
 ou d'un sel pharmaceutiquement acceptable de ce composé.

11. Utilisation d'un composé suivant l'une quelconque des revendications précédentes dans la préparation
 10 d'un médicament destiné au traitement de l'apoplexie, de l'épilepsie ou des syndromes de psychose
 épileptiques, l'hypertension, l'angor, la migraine, l'arythmie, la thrombose, l'embolie, la crise cardiaque
 aiguë, le syndrome d'irritation intestinale, des troubles de dégénérescence nerveuse tels que la
 chorée d'Alzheimer ou d'Huntington, la diurèse, l'ischémie telle que l'ischémie focale et globale ou
 l'ischémie cérébrovasculaire induite par l'abus de la cocaïne, ou une lésion de la moelle épinière.

15 12. Procédé qui comprend la préparation d'une formulation pharmaceutique renfermant un composé
 suivant l'une quelconque des revendications 1 à 10 et un excipient acceptable du point de vue
 pharmaceutique.

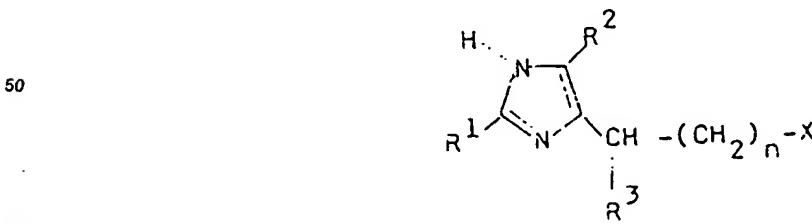
20 13. Procédé de préparation d'un composé de formule A



FORMULE A

dans laquelle

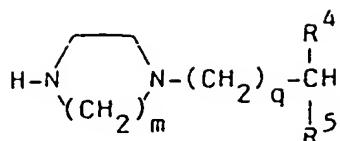
35 R¹ est un groupe aryle ;
 R² est un groupe aryle, alkyle inférieur ou l'hydrogène ;
 R³ est un groupe alkyle inférieur, hydroxy ou l'hydrogène ;
 R⁴ est un groupe aryle ;
 R⁵ est un groupe aryle ;
 40 m a la valeur deux ou trois ;
 n a la valeur zéro, un ou deux,
 sous réserve que lorsque R³ est un groupe hydroxy, n soit égal à un ou deux ; et
 q a la valeur zéro, un, deux ou trois ;
 et de ses sels acceptables du point de vue pharmaceutique, qui consiste
 45 (a) à condenser un composé de formule



dans laquelle n, R¹ et R² ont la définition indiquée ci-dessus, R³ est l'hydrogène ou un groupe alkyle inférieur et X est un atome d'halogène,

avec un composé de formule

5

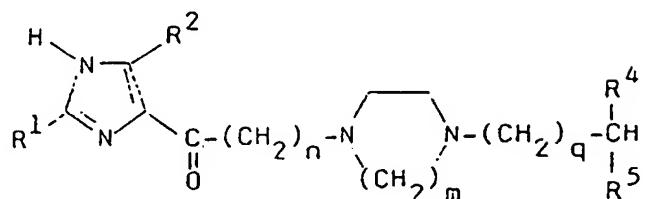


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dans laquelle m , q , R^4 et R^5 sont tels que définis ci-dessus ; ou bien
b) à réduire un composé de formule

15

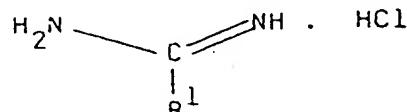
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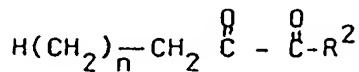
dans laquelle R^1 , R^2 , R^4 , R^5 , m et q sont tels que définis ci-dessus et n est égal à un ou deux,
pour former un composé de formule A dans laquelle R^3 est un groupe hydroxy ; ou bien
c) à faire réagir un composé de formule

30



dans laquelle R^1 est tel que défini ci-dessus, avec un composé de formule

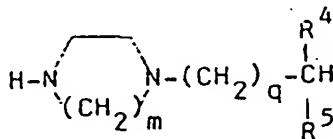
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dans laquelle n et R^2 sont tels que définis ci-dessus, et un composé de formule

45



50

dans laquelle m , q , R^4 et R^5 sont tels que définis ci-dessus, pour former un composé de formule A

dans laquelle R^3 est l'hydrogène ; ou bien

d) à convertir un composé sous la forme base libre de formule A en son sel d'addition d'acide ; ou bien

e) à convertir un sel d'addition d'acide d'un composé de formule A en un composé sous la forme base libre de formule A ; ou bien

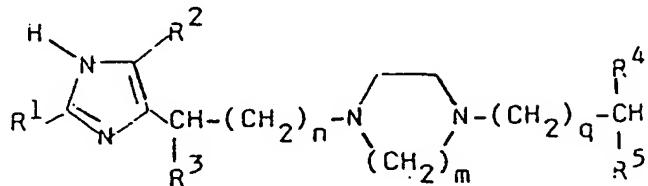
f) à convertir un sel d'addition d'acide d'un composé de formule A en un autre sel d'addition d'acide d'un composé de formule A.

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung mit einer Struktur, die durch die Formel:

5

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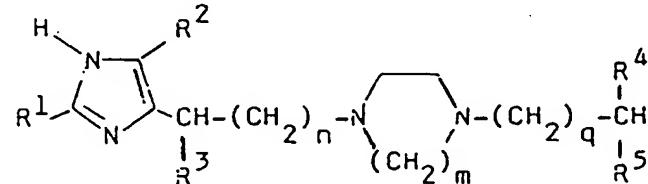


dargestellt wird, worin:

15 R¹ Aryl ist;
 R² Aryl, C₁-4-Alkyl oder Wasserstoff ist;
 R³ C₁-4-Alkyl, Hydroxy oder Wasserstoff ist;
 R⁴ Aryl ist;
 R⁵ Aryl ist;
 20 m zwei oder drei ist;
 n null, eins oder zwei ist, mit der Maßgabe, daß wenn R³ Hydroxy ist, n eins oder zwei ist; und
 q null, eins, zwei oder drei ist;
 oder ein pharmazeutisch annehmbares Salz davon.

25 2. Verbindung nach Anspruch 1, worin m zwei ist, q null ist, n null ist und R² Methyl bedeutet.3. Verbindung nach Anspruch 2, worin R³ Wasserstoff bedeutet.4. Verbindung nach Anspruch 1, worin R³ Niederalkyl oder Hydroxy darstellt.30 5. Verbindung nach Anspruch 3, worin R¹ 4-Methylphenyl bedeutet.6. Verbindung nach Anspruch 5, worin R⁴ und R⁵ 4-Chlorphenyl oder 4-Fluorphenyl sind.35 7. Verbindung nach Anspruch 2, worin R¹ 3-Trifluormethylphenyl, 4-Methoxyphenyl, 4-Chlorphenyl, 3,4-Dimethoxyphenyl, 3-Chlorphenyl oder Phenyl darstellt.8. Verbindung nach Anspruch 1, worin m 3 ist.40 9. Verbindung, ausgewählt aus 1-Diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazin, 1-Diphenylmethyl-4-[(2-phenyl-1H-imidazol-4-yl)methyl]piperazin, 1-Diphenylmethyl-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazin und pharmazeutisch annehmbaren Säureadditionssalzen davon.45 10. Verbindung mit der Struktur, die durch die Formel:

50



55

dargestellt wird, worin:

R¹ Aryl ist;
 R² Aryl oder C₁-4-Alkyl ist;

R³ C₁₋₄-Alkyl, Hydroxy oder Wasserstoff ist;

R⁴ Aryl ist;

R⁵ Aryl ist;

m zwei oder drei ist;

5 n null, eins oder zwei ist, mit der Maßgabe, daß wenn R³ Hydroxy ist, n eins oder zwei ist; und

q null, eins, zwei oder drei ist;

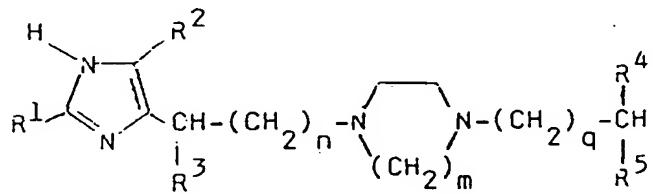
oder ein pharmazeutisch annehmbares Salz davon.

11. Verwendung einer Verbindung nach irgendeinem der vorangehenden Ansprüche für die Herstellung eines Medikaments zur Behandlung von Schlaganfall, Epilepsie oder epileptisch psychotischen Symptomen, Hochdruck, Angina, Migräne, Arrhythmie, Thrombose, Embolie, akutem Herzversagen, Reizdarm-Syndrom, neurodegenerativen Krankheiten wie z.B. Alzheimer oder Chorea Huntington, Diurese, Ischämie, wie z.B. fokaler und globaler Ischämie oder durch Kokain-Mißbrauch induzierter cerebrovaskulärer Ischämie, oder spinaler Verletzung.

15 12. Verbindung nach irgendeinem der Ansprüche 1 bis 10 zur pharmazeutischen Verwendung.

13. Pharmazeutische Formulierung, umfassend eine Verbindung nach irgendeinem der Ansprüche 1 bis 10 und einen pharmazeutisch annehmbaren Exzipienten.

20 14. Verfahren zur Herstellung einer Verbindung der Formel A



Formel A

35 worin:

R¹ Aryl ist;

R² Aryl, Niederalkyl oder Wasserstoff ist;

R³ Niederalkyl, Hydroxy oder Wasserstoff ist;

R⁴ Aryl ist;

40 R⁵ Aryl ist;

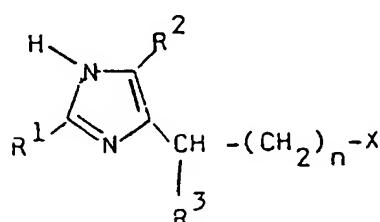
m zwei oder drei ist;

n null, eins oder zwei ist, mit der Maßgabe, daß wenn R³ Hydroxy ist, n eins oder zwei ist; und

q null, eins, zwei oder drei ist;

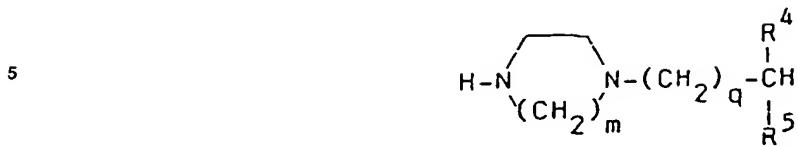
und der pharmazeutisch annehmbaren Salze davon, welches umfaßt

45 (a) Kondensation einer Verbindung der Formel

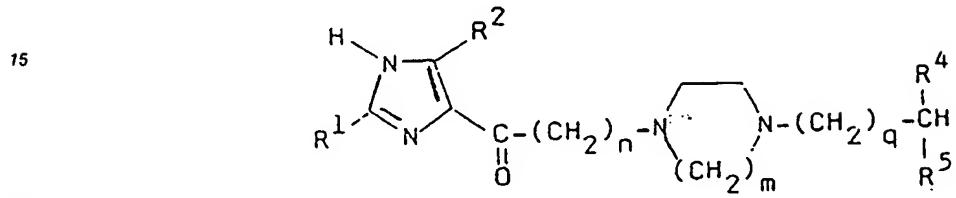


worin n, R¹ und R² wie oben definiert sind, R³ Wasserstoff oder Niederalkyl ist und X ein Halogenatom darstellt,

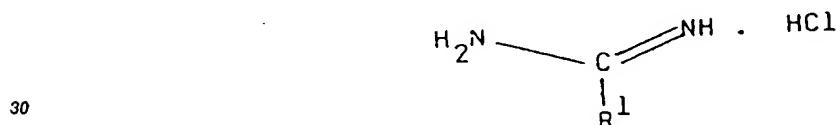
mit einer Verbindung der Formel



10 worin m, q, R⁴ und R⁵ wie oben definiert sind; oder
(b) Reduktion einer Verbindung der Formel



worin R¹, R², R⁴, R⁵, m und q wie oben definiert sind und n eins oder zwei ist,
um eine Verbindung der Formel A zu bilden, worin R³ Hydroxy ist;
oder
25 (c) Umsetzung einer Verbindung der Formel



worin R¹ wie oben definiert ist, mit einer Verbindung der Formel



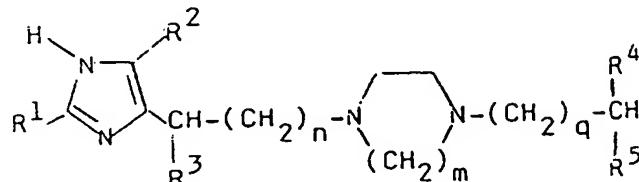
40 worin n und R² wie oben definiert sind, und einer Verbindung der Formel



worin m, q, R⁴ und R⁵ wie oben definiert sind, um eine Verbindung der Formel A zu bilden, worin R³
50 Wasserstoff ist; oder
(d) Umwandlung einer freien Base-Verbindung der Formel A in deren Säureadditionssalz; oder
(e) Umwandlung eines Säureadditionssalzes einer Verbindung der Formel A in eine freie Base-
Verbindung der Formel A; oder
55 (f) Umwandlung eines Säureadditionssalzes einer Verbindung der Formel A in ein anderes Säuread-
ditionssalz einer Verbindung der Formel A.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren, welches umfaßt die Herstellung einer Verbindung mit der Struktur, die durch die Formel



dargestellt wird, worin:

R¹ Aryl ist;

R² Aryl, C₁-4-Alkyl oder Wasserstoff ist;

R³ C₁-4-Alkyl, Hydroxy oder Wasserstoff ist;

R⁴ Aryl ist;

R⁵ Aryl ist;

m zwei oder drei ist;

n null, eins oder zwei ist, mit der Maßgabe, daß wenn R³ Hydroxy ist, n eins oder zwei ist; und

20 q null, eins, zwei oder drei ist;

oder eines pharmazeutisch annehmbaren Salzes davon.

2. Verfahren nach Anspruch 1, worin m zwei ist, q null ist, n null ist und R² Methyl darstellt.

25 3. Verfahren nach Anspruch 2, worin R³ Wasserstoff ist.

4. Verfahren nach Anspruch 1, worin R³ Niederalkyl oder Hydroxy ist.

5. Verfahren nach Anspruch 3, worin R¹ 4-Methylphenyl ist.

30 6. Verfahren nach Anspruch 5, worin R⁴ und R⁵ 4-Chlorphenyl oder 4-Fluorphenyl darstellen.

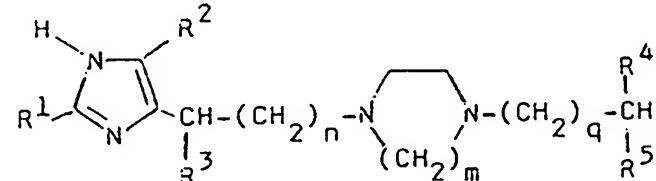
7. Verfahren nach Anspruch 2, worin R¹ 3-Trifluormethylphenyl, 4-Methoxyphenyl, 4-Chlorphenyl, 3,4-Dimethoxyphenyl, 3-Chlorphenyl oder Phenyl darstellt.

35 8. Verfahren nach Anspruch 1, worin m 3 ist.

9. Verfahren, welches umfaßt die Herstellung einer Verbindung, die ausgewählt ist aus 1-Diphenylmethyl-4-[(2-(4-methylphenyl)-5-methyl-1H-imidazol-4-yl)methyl]piperazin, 1-Diphenylmethyl-4-[(2-phenyl-1H-imidazol-4-yl)methyl]piperazin, 1-Diphenylmethyl-4-[(2-phenyl-5-methyl-1H-imidazol-4-yl)methyl]piperazin und pharmazeutisch annehmbaren Säureadditionssalzen davon.

40 10. Verfahren, welches umfaßt die Herstellung einer Verbindung mit der Struktur, die dargestellt wird durch die Formel:

45



55 worin:

R¹ Aryl ist;

R² Aryl oder C₁-4-Alkyl ist;

R³ C₁-4-Alkyl, Hydroxy oder Wasserstoff ist;

R⁴ Aryl ist;R⁵ Aryl ist;

m zwei oder drei ist;

n null, eins oder zwei ist, mit der Maßgabe, daß wenn R³ Hydroxy ist, n eins oder zwei ist; und

5 q null, eins, zwei oder drei ist;

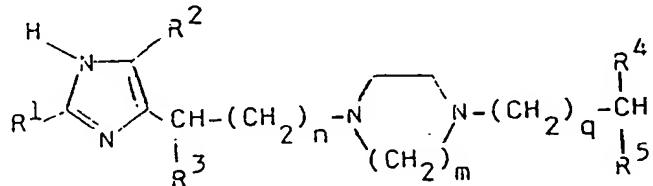
oder eines pharmazeutisch annehmbaren Salzes davon.

11. Verwendung einer Verbindung nach irgendeinem der vorangehenden Ansprüche bei der Herstellung eines Medikaments für die Behandlung von Schlaganfall, Epilepsie oder epileptisch psychotischen Symptomen, Hochdruck, Angina, Migräne, Arrhythmie, Thrombose, Embolie, akutem Herzversagen, Reizdarm-Syndrom, neurodegenerativen Erkrankungen wie z.B. Alzheimer oder Chorea Huntington, Diurese, Ischämie, wie z.B. fokaler und globaler Ischämie oder durch Kokain-Mißbrauch induzierter cerebrovaskulärer Ischämie, oder spinaler Verletzung.

15 12. Verfahren, welches umfaßt die Herstellung einer pharmazeutischen Formulierung, die eine Verbindung nach irgendeinem der Ansprüche 1 bis 10 und einen pharmazeutisch annehmbaren Exzipienten umfaßt.

13. Verfahren zur Herstellung einer Verbindung der Formel A

20



Formel A

30

worin:

R¹ Aryl ist;R² Aryl, Niederalkyl oder Wasserstoff ist;R³ Niederalkyl, Hydroxy oder Wasserstoff ist;35 R⁴ Aryl ist;R⁵ Aryl ist;

m zwei oder drei ist;

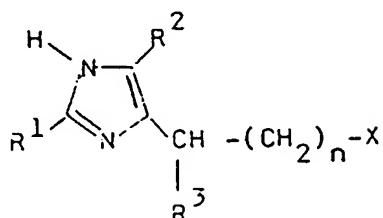
n null, eins oder zwei ist, mit der Maßgabe, daß wenn R³ Hydroxy ist, n eins oder zwei ist; und

q null, eins, zwei oder drei ist;

40 und der pharmazeutisch annehmbaren Salze davon, welches umfaßt

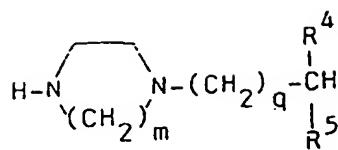
(a) Kondensation einer Verbindung der Formel

45



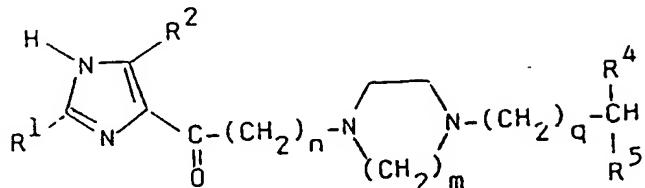
50

worin n, R¹ und R² wie oben definiert sind, R³ Wasserstoff oder Niederalkyl ist und X ein Halogenatom darstellt,
55 mit einer Verbindung der Formel



worin m , q , R^4 und R^5 wie oben definiert sind; oder
 (b) Reduktion einer Verbindung der Formel

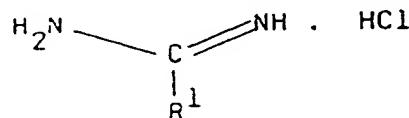
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20

worin R^1 , R^2 , R^4 , R^5 , m und q wie oben definiert sind und n eins oder zwei ist,
 um eine Verbindung der Formel A zu bilden, worin R^3 Hydroxy ist;
 oder
 (c) Umsetzung einer Verbindung der Formel

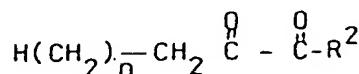
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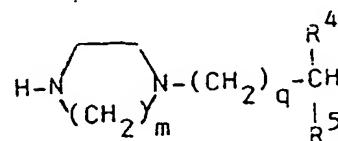
worin R^1 wie oben definiert ist, mit einer Verbindung der Formel

35



worin n und R^2 wie oben definiert sind, und einer Verbindung der Formel

40



45

worin m , q , R^4 und R^5 wie oben definiert sind, um eine Verbindung der Formel A zu bilden, worin R^3 Wasserstoff ist; oder
 (d) Umwandlung einer freien Base-Verbindung der Formel A in deren Säureadditionssalz; oder
 (e) Umwandlung eines Säureadditionssalzes einer Verbindung der Formel A in eine freie Base-Verbindung der Formel A; oder
 (f) Umwandlung eines Säureadditionssalzes einer Verbindung der Formel A in ein anderes Säureadditionssalz einer Verbindung der Formel A.

55